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Chapter

32

Postmenopausal Osteoporosis

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Introduction

Aging is a non-homogenous process, where progressive and broadly predictable changes begin and are associated with increased susceptibility to many diseases. Genetics, lifestyle, and environment play an influential role in aging.

Osteoporosis (OP) is a topic neglected by general population. Merely giving painkillers and calcium and vitamin D will not suffice after confirmation of diagnosis of menopause and osteoporosis.

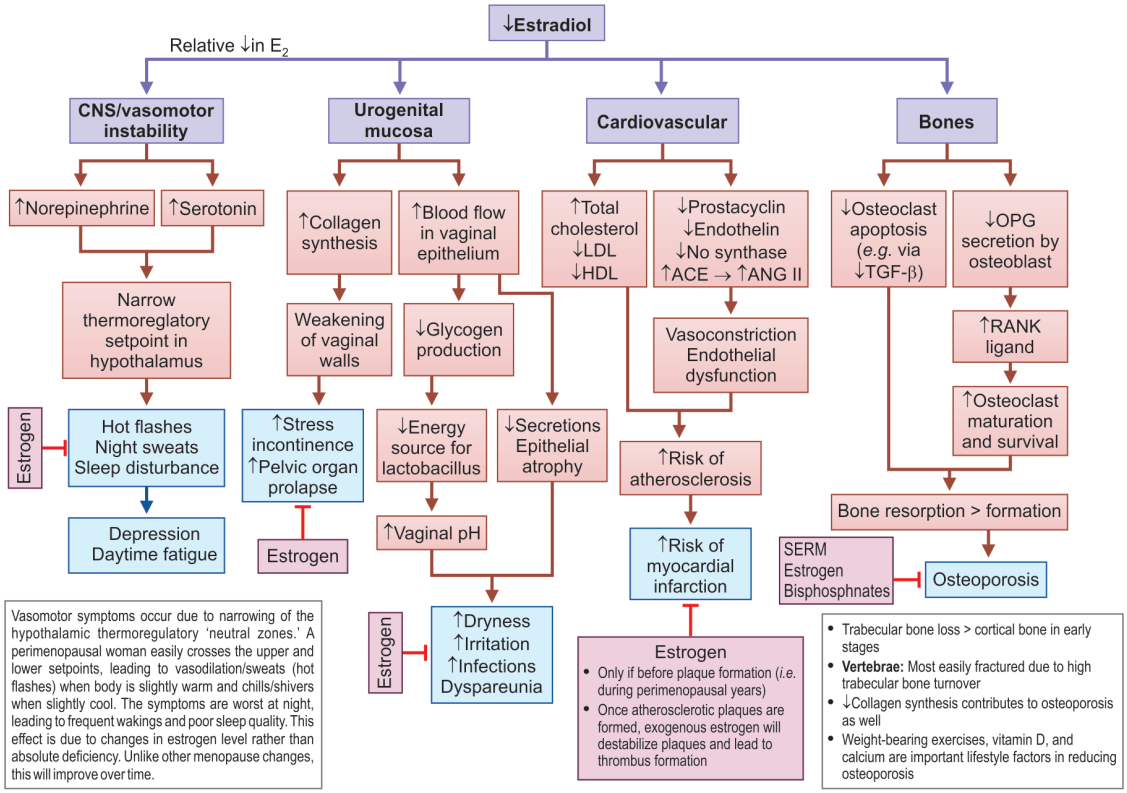
When bone density is reduced, altered bone architecture and reduced bone production happens. Osteoporosis affects both males and females also.

It commonly happens after menopause due to sudden decrease in oestrogen. Chances of fracture will be there if it has not treated or prevented. Even small fall or minor knock will be responsible for fracture.

CAUSES OF OSTEOPOROSIS

- Calcium is essential for proper functioning of the heart, brain, and other organs. To keep those critical organs functioning, the body reabsorbs calcium that is stored in the bones to maintain blood calcium levels. If calcium intake is not sufficient or if the body does not absorb enough calcium from the diet, bone production and bone tissue may suffer. Thus, the bones may become weaker, resulting in fragile and brittle bones that can break easily. Inadequate intake of calcium and vitamin D and lack of weight-bearing exercise is also associated with age-related bone changes.
- The leading cause of osteoporosis is a lack of certain hormones, like oestrogen in women and androgen in men. Women, especially those older than 60 years of age, are frequently diagnosed with the disease. E_2 falls 2 years preceding the final menstrual period and is persistently low in the following 12-month period of amenorrhea, whilst follicle-stimulating hormone (FSH) continue to rise. In postmenopausal women, estrone (E_1), generated through the conversion of androgens (secreted by the adrenal glands and postmenopausal ovaries) in the adipose tissue and liver, predominates in the circulation. It is believed to be the main cause that contributes to bone loss in this age group.
- Overuse of corticosteroids (Cushing syndrome), thyroid problems, lack of muscle use, bone cancer, certain genetic disorders, use of certain medications, and problems such as low calcium in the diet.
- Women who are postmenopausal, including those who have had early

Flowchart 32.1: Menopausal symptoms



Sources: Lentz: Comptrehensive Gynecology, 6E, Williams Textbook of Endocrinology, 12E

or surgically-induced menopause, or abnormal or absence of menstrual periods, are at greater risk.

- Cigarette smoking, eating disorders, such as anorexia nervosa or bulimia, low amounts of calcium in the diet, heavy alcohol consumption, inactive lifestyle, and use of certain medications, such as corticosteroids and anticonvulsants, are also risk factors.
- Rheumatoid arthritis itself is a risk factor for osteoporosis.
- History of osteoporosis to parents is a risk factor for the offspring.

Investigations

Workup consists of appropriate laboratory studies to establish baseline values and to look for potential secondary causes of osteoporosis, along with measurement of bone mineral density (BMD) to assess bone loss and estimate the risk of fracture. Bone biopsy may be indicated in specific situations. Conventional radiography is used for the qualitative and semi-quantitative evaluation of osteoporosis; morphometry assesses the presence of fractures.

Quantitative imaging methods commonly used are—dual-energy X-ray absorptiometry (DXA or DEXA) and quantitative computed tomography (QCT) scanning. In the United States, current diagnostic and treatment criteria for osteoporosis are based solely on QCT hip and DXA spine or hip T-score measurements.

Two types of devices can carry out a DEXA scan:

- *A central device:* A hospital-based scan measures hip and spine BMD, while the patient lies on a table.
- *A peripheral device:* A mobile machine that tests bone in the wrist, heel, or finger.

Bone Mineral Density Screening (Fig. 32.1)

WHO defines osteoporosis as a "systemic skeletal disease characterized by low bone mass (measured as BMD) and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture and involves the wrist, spine, hip, pelvis, ribs or humerus."

As per American College of Obstetricians and Gynecologists (ACOG), BMD testing is recommended for diagnosis of osteoporosis. ACOG recommends BMD testing to be performed based on patients risk factors. It should be done only if it affects the treatment. BMD testing is recommended for all postmenopausal women and age above 65 years. Below the age of 65 years, BMD testing is recommended if patient is postmenopausal and has risk factors. Epidemiological data suggests that for women below 60 years, osteoporosis screening and treatment would be inefficient. The frequency of screening should not be more than once in 2 years.[6] In India opportunistic screen is recommended above 40 years by Indian menopause society.

DXA is the gold standard for measuring BMD, as it is accurate, precise measures at important sites and is not expensive relatively and has moderate exposure to radiation. In DEXA, two beams of X-ray are projected on the site. The amount of the X-ray beam that is blocked by the bone and soft tissue are compared to estimate the bone density. DEXA screening is fast and exposes the person to a low dose of radiation. BMD results are expressed based on standard deviation (SD) units from the population mean in young adults (T-score) or from the mean in an age matched population (Z-score). World Health Organisation (WHO) and International Osteoporosis Foundation recommended the T-score in post-menopausal women based on the National Health and Nutrition Examination Survey III reference database, conducted in Caucasian women in the 20–29 years age group (Fig. 32.2). The T-score is measured at lumbar and two hip sites (femoral neck and total hip). Osteoporosis was defined as a T-score ≤–2.5 at any of the three sites. Osteopenia is defined as the T-score between –2.5 to –1 (not inclusive) at any site.

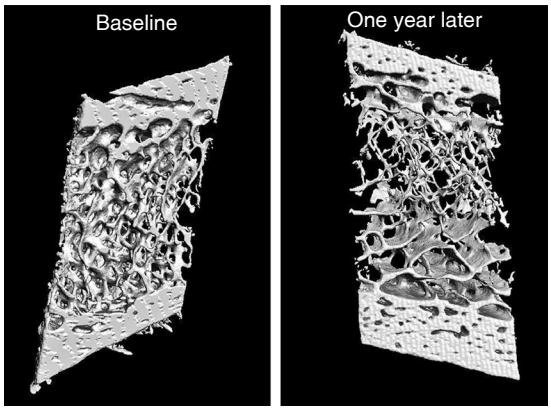


Fig. 32.1: Change in bone in untreated post-menopausal women

The results of the test are given as a DEXA T-score or a Z-score.

The Z-score describes the SD variation by which the BMD in an individual differs from the mean expected for a particular age group and sex. This is used in pre-adolescent and premenopausal women. Z-score below –2 is abnormal and is low for age.

Other methods for BMD screening like peripheral bone densitometry including ultrasonography (USG), single energy X-ray absorptiometry, peripheral DEXA (P-DEXA) and peripheral quantitative tomography are cheaper, portable and involve less radiation. They only assess peripheral skeleton and cannot replace DEXA.

P-DEXA is a modification of DEXA. It measures bone density in peripheral bones like wrist. Radiation dose is low.

Quantitative CT is accurate but involves higher dose of radiation.

In USG, sound waves bounce off the bone. It is usually done at the heel. It is quick and not harmful.

Dual photon absorptiometry is another method that uses a radioactive substance.

To collate and consider all factors, WHO has an absolute fracture prediction algorithm (FRAX), which use a computer-based tool to estimate patients 10 years fracture risk. It takes into consideration BMD and other personal and family history. Treatment is recommended for women with 10 years fracture probability of 3% or more. The test is repeated every 2 years, as this allows for comparison between results.

Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover reflect bone formation or bone resorption. These markers (both formation and resorption) may be elevated in high-bone turnover states (*e.g.* early postmenopausal osteoporosis) and may be useful in some patients for monitoring early response to therapy.

Currently available serum markers of bone formation (osteoblast products) include the following:

- Bone-specific alkaline phosphatase (BSAP)
- Osteocalcin (OC)
- Carboxyterminal propeptide of type I collagen (PICP)
- Aminoterminal propeptide of type I collagen (PINP)

Currently available urinary markers of bone resorption (osteoclast products) include the following:

- Hydroxyproline
- Free and total pyridinolines (Pyd)
- Free and total deoxypyridinolines (Dpd)
- N-telopeptide of collagen cross-links (NTx) (also available as a serum marker)
- C-telopeptide of collagen cross-links (CTx) (also available as a serum marker)

Currently available serum markers of bone resorption include cross-linked ctelopeptide of type I collagen (ICTP) and tartrate-resistant acid phosphatase, as well as NTx and CTx. Of all the biochemical markers of bone turnover mentioned above, the ones most commonly used in clinical practice are BSAP, OC, urinary NTx, and serum CTx. BSAP can be mildly elevated in patients with fractures. In addition, patients with hyperparathyroidism, Paget disease, or osteomalacia can have elevations of BSAP. Serum OC levels, if high, indicate a high-turnover type of osteoporosis. Elevation of urinary NTx (>40 nmol bone collagen equivalent per mmol urinary creatine) indicates a high turnover state. Significant controversy exists regarding the use of these biochemical markers, and concerns have been raised about intra-assay and interassay variability. Further study is needed to determine the clinical utility of these markers in osteoporosis management. Plain radiography is recommended to assess overall skeletal integrity. In particular, in the workup for osteoporosis, plain radiography may be indicated if a fracture is already suspected or if patients have lost more than 1.5 inches of height.

TREATMENT OF OSTEOPOROSIS

Treatment aims to:

- Slow or prevent the development of osteoporosis
- Maintain healthy bone mineral density and bone mass
- Prevent fractures
- Reduce pain
- Maximize the person's ability to continue with their daily life
- Fracture management
  1. Relieve pain
  2. Stabilise fracture and restore anatomy
  3. Manage co-morbidities
  4. Restore level of function and mobility
  5. Psychosocial support

This is done through preventive lifestyle measure and the use of supplements and drugs.

Whom to Treat

a. Fragility fractures [clinical, height loss of >4 cm, kyphosis or morphometric by X-rays or vertebral fractures assessment (VFA) by DXA]

b. BMD T-scores ≤–2.5 at the femoral neck or spine, wrist by DXA
c. Women with low bone mass by DXA with one major or two other risk factors or eligible by fracture risk assessment tool (FRAX).

Drug Therapy (Tables 32.1, 32.2 and Flowcharts 32.2, 32.3)

Drugs that can help prevent and treat osteoporosis include:

- Substrates for bone formation—nutrients
- Drugs which inhibit bone resorption—antiresorptive agents
- Drugs which stimulate bone formation—bone anabolic agents

Drugs that can help prevent and treat osteoporosis include:

1. Bisphosphonates—alendronate, risedronate ibandronate, zoledronate. These are antiresorptive drugs that slow bone loss and reduce fracture risk.
2. Menopausal hormone therapy (MHT)
3. Estrogen agonists or antagonists, also known as selective estrogen-receptor modulators, SERMs), *e.g.* raloxifene: These can reduce the risk of spine fractures in women after menopause.
4. *Calcitonin:* This helps prevent spinal fracture in postmenopausal women, and it can help manage pain if a fracture occurs.
5. *Parathyroid hormone:* For example, teriparatide—antiresorptive. This is approved for people with a high risk of fracture, as it stimulates bone formation.
6. Receptor activator of nuclear factor kappa-β (NF-κβ) ligand [*RANK ligand (RANKL)] inhibitors, such as denosumab:* This is an immune therapy and a new type of osteoporosis treatment. Other types of oestrogen and hormone therapy may help.

Choice of Medication

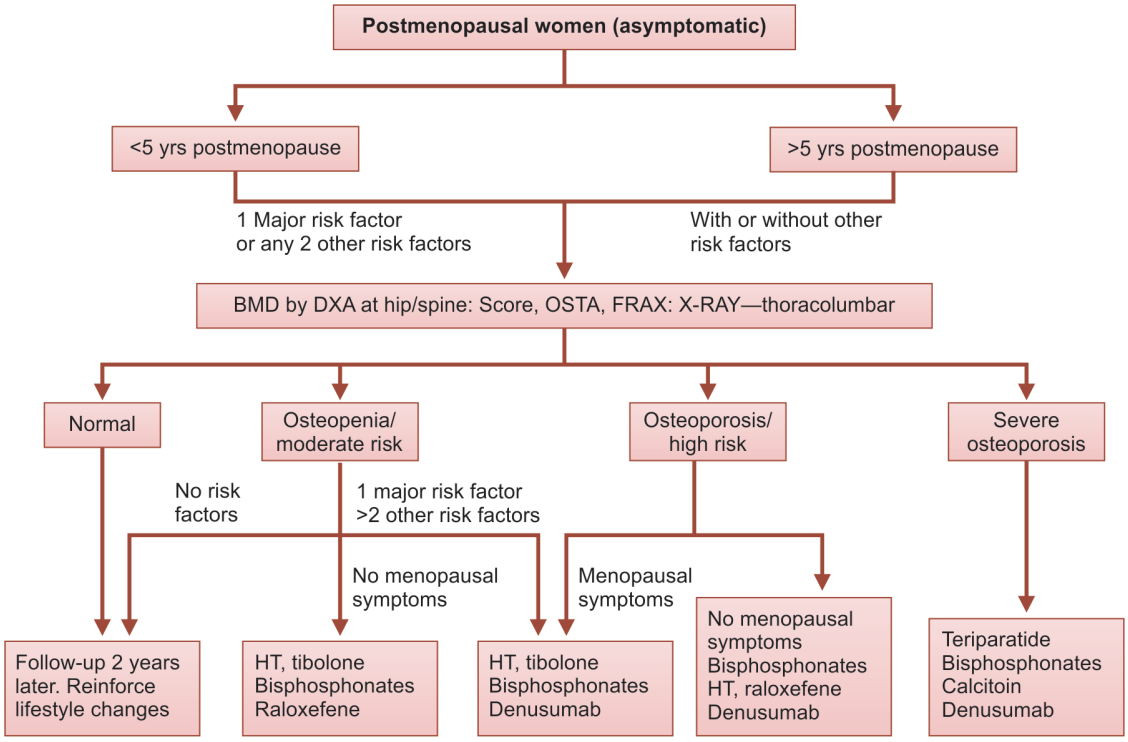
Depends on

- Drug-related (risk-benefit)
- Patient profile (age, years since menopause, symptoms, comorbidities)
- Environment-related factors (economics and social)
- Patients should be educated in patient management orders (PMO) and its treatment and empowered to take part in shared decision-making to improve adherence.

Table 32.1: FDA approved drugs for osteoporosis

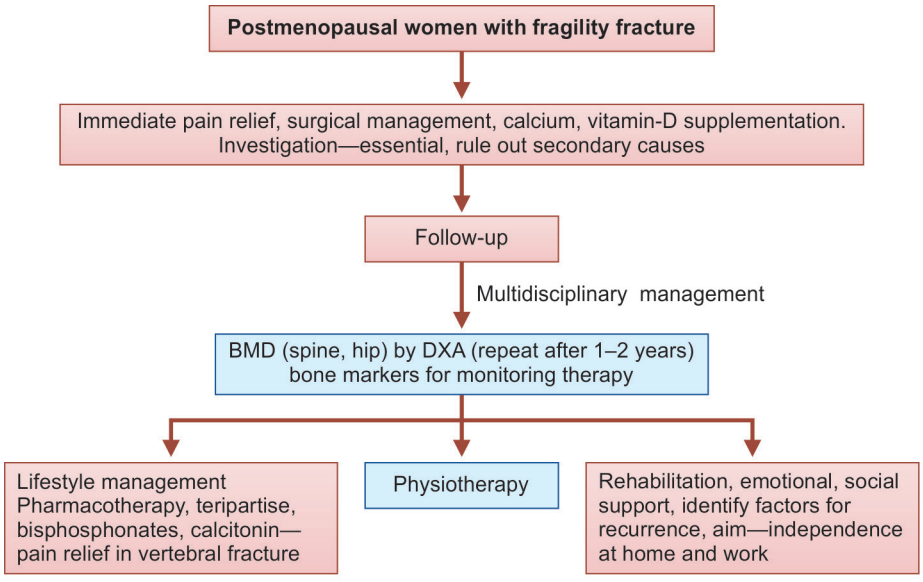
Drugs	*Prevention*	*Treatment*
Alendronate	5 mg, PO, daily 35 mg, PO, weekly	10 mg, PO, daily 70 mg, PO, weekly 70 mg + D, daily
Risedronate	5 mg, PO, daily 35 mg, PO, weekly 150 mg, PO, monthly	5 mg, PO, daily 35 mg, PO, weekly 150 mg, PO, monthly
Ibandronate	2.5 mg, PO, daily 150 mg, monthly	2.5 mg, PO, daily 150 mg, monthly 3 mg, IV, q3mo
Zoledronic acid	5 mg, IV, q2yrs	5 mg, IV, q1yr
Estrogen	Multiple formulations/regimens	—
Raloxifene	60 mg, PO, daily	60 mg, PO, daily
Calcitonin	—	200 IU, intranasal, OD or 100 IU, SC
Denosumab	—	60 mg, SC q6mo
Teriparatide	—	20 µg, SC OD for up to 24 mo

Flowchart 32.2: Osteoporosis risk analysis



Sources: Meeta, Harinarayan CV, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical practice guidlelines on postmenopausal osteoporosis: Indian Menopause Society, 2019

Flowchart 32.3: Management of women with fragility fractures



Sources: Lentz: Comptrehensive Gynecology, 6E Williams Textbook of Endocrinology, 12E

Table 32.2: Antiresorptive drugs for osteoporosis

Drugs	*Dose*	*Efficacy*	*Advantages*	*Disadvantages*
Estrogen (CEE)	0.625–1.25 mg/day	Vertebral and non-vertebral BMD ↓Vertebral and hip fractures by 33–50%	Physiologic test of menopausal symptoms	Need for early use (<5 yrs) AEs on endometrium breast, CVS
Oral bisphosphonates (alendronate) Ibandronate	5–10 mg/day 35–70 mg/wk 150 mg/mo	Vertebral and non-vertebral BMD 5–10% ↓Verbebral and non-vertebral fractures by 40–50% ↓Vertebral fracture 62% no change in non-vertebral	Once weekly dose 10-yr safety record Lasting benefits (up to 2 yrs after withdrawal)	Upper GI side effects Precautions Contraindications (renal failure) Atypical femur fractures Osteonecrosis of jaw
IV bisphosphonate	5 mg, yearly for 3–6 yrs	↓Vertebral fracture 70%	Yearly dose complicance	Acute flue-like syndrome
SERMs (raloxifene)	60 mg/day	↓Vertebral fractures: 30–50% BMD in spine and femoral neck by 2.5%	Bone selective No endometrial effects Anti-mitotic on breast	DVT Hot flashes No effect on non-vertebral fractures
Salmon calcitonin	200 µg nasal	36% ↓vertebral fractures in older PM women No effects on non-vertebral fractures		
Denosumab	60 mg twice a year sc	↓Vertebral fractures 68% ↓Hip fracture 40% ↓Non-vertebral fracture 20%	Only twice a year self administration	Infections Rare atypical femur fractures Osteonecrosis of jaw

Table 32.3: BMD response

Medication	*Spine*	*Hip*
Estrogen	↑↑	↑
Alendronate	↑↑↑	↑↑
Risedronate	↑↑↑	↑↑
Ibandronate	↑↑↑	↑↑
Zoledronic acid	↑↑↑	↑↑
Calcitonin	~	~
Raloxifene	↑	(↑)
Denosumab	↑↑↑	↑↑
Teriparatide	↑↑↑↑	↑

BMD: Bone mineral density

Challenges of Treatment

- Economics
- Long-term compliance
- Side effects.

Despite major advances in diagnosis and therapy, most patients with osteoporosis receive no evaluation or treatment, even patients who have had a fragility fracture.

I. Bisphosphonates

Most widely used drugs. Effect on bone resorption persists after discontinuation (unique to bisphosphonate). It should be consumed empty stomach with glass of water. Do not bend for 30 minutes.

Safety data available for 10 years. Serum calcium and serum creatinine should be measured before starting therapy. Patient should be calcium and vitamin D replete **(Figs 32.2, 32.3 and Flowcharts 32.3, 32.4)**.

Side effects:

- GI intolerance (oral)
- Hypocalcemia
- Renal dysfunction
- Acute phase reaction—flu-like symptoms (myalgia, arthralgia, fever) common in 12–48 hours after IV dosing, lasts usually for 1–2 days, sometimes 1 week.
- Osteonecrosis of the jaw
- Atypical fractures.

Monitoring therapy **(Flowchart 32.4)**

- BMD by DEXA—repeat after 1 year of therapy
- Bone turnover markers
- Resorption markers after 3–6 months after treatment initiation
- Formation markers—6 months after treatment initiation

Non-responders to therapy: May be due to:

- Poor adherence
- Poor calcium/vitamin-D health
- Untreated secondary osteoporosis
- Concomitant therapy with skeletotropic drugs
- Inappropriate choice of drugs, or wrong choice of monitoring strategies (GRADE C). There are no head-to-head trials of the various drugs comparing their effects on fracture rates.

II. Menopausal Hormone Therapy

Most prolonged and most predictable dose and duration-dependent increase in bone density with estrogen. Effective in preventing osteoporotic fractures of the hip and spine in a study of low and mixed risk women. EPT/ET is a cost effective first line therapy in early postmenopausal women at risk for osteoporosis unless contraindicated (GRADE A). Estrogen progesterone therapy (EPT)/ estrogen therapy (ET) may be used for prevention and treatment of osteoporosis in the early post-menopause in symptomatic women unless there is a contraindication.

ET/EPT prevents all osteoporotic fractures even in low-risk population, it increases lumbar spine BMD up to 7.6% and femoral neck BMD up to 4.5% over 3 years. It reduces the risk of spine, hip, and other osteoporotic fractures by 33–40% (GRADE A).

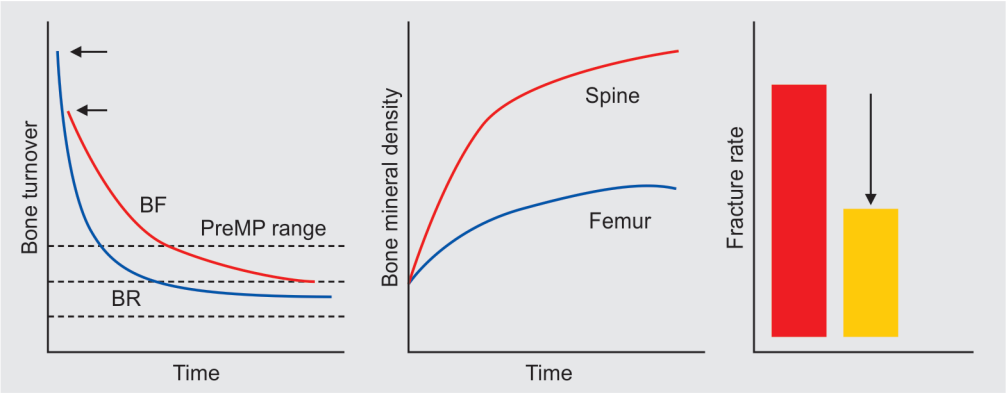
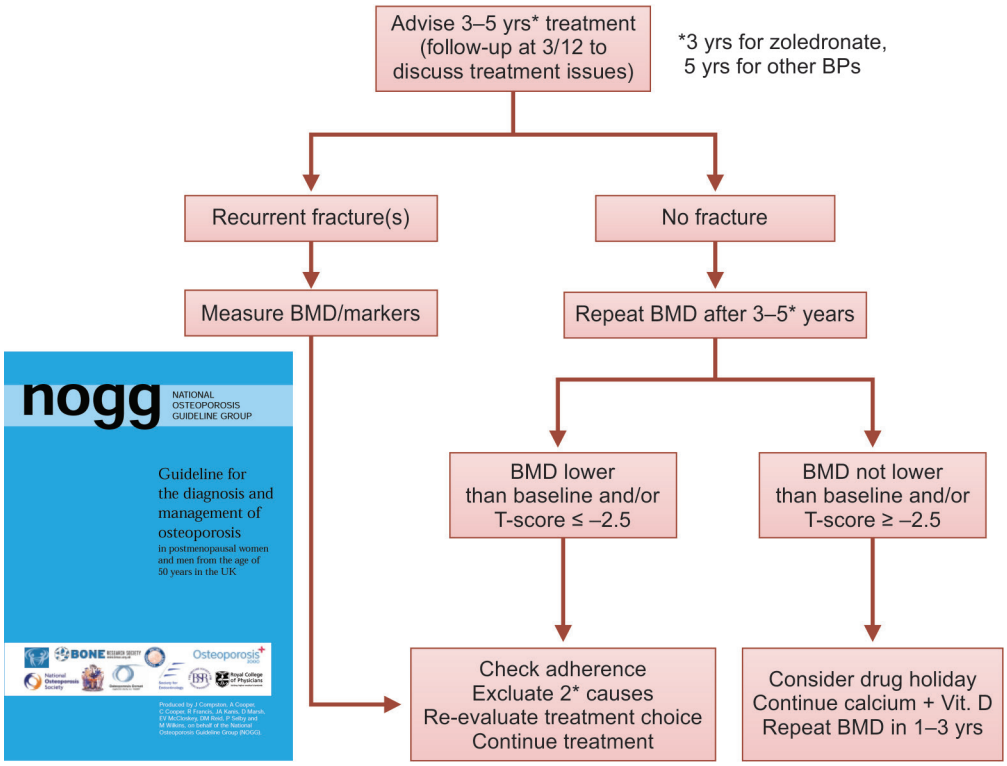


Fig. 32.2: Bisphosphonates—alendronate, risedronate, ibandronate, zoledronic acid

Flowchart 32.4: Bisphosphonates—algorithm for long-term treatment



Progestogens should be added to ET in women with uterus (GRADE A).

- Hormone therapy (HT) should not be started solely for bone protection after 10 years of menopause. Extended use of HT in women with reduced bone mass is an option after considering the risk–benefit analysis compared to the other available therapies for osteoporosis. The bone protective effect is lost after stopping HT (GRADE B).
- HT is indicated as primary therapy to prevent bone loss in women with premature menopause and secondary amenorrhea (GRADE C).

Side effects:

- Increased risk of deep vein thrombosis (DVT)
- Not recommended to initiate therapy above age 60
- Extended use possibly associated with increased diagnosis of breast cancer [only combined hormone replacement therapy (HRT)]
- Cessation of therapy unpredictable effect

III. Tibolone

It has an estrogenic effect on bone, inhibiting bone resorption by reducing osteoclastic activity. Tibolone is approved in 90 countries to treat menopausal symptoms. We recommend that tibolone is prescribed in a single daily dose of 2.5 mg orally. A lower dose of 1.25 mg has been found to be equally effective for most indications, including osteoporosis (GRADE A).

IV. Raloxifene

Acts as an agonist in bone and lipid metabolism. And as a Antagonist at uterine

endometrium and at breast tissue. Hence, used in treatment and prevention of postmenopausal osteoporosis.

Role of raloxifene is being evaluated in:

- Advanced breast cancer
- Chemoprevention of breast cancer
- Cardioprotection.

Benefit:

- Prevents vertebral fractures
- Prevents estrogen receptor positive (ER+) breast
- Has a favorable effect on lipid profile
- Has no effect on risk for coronary events.

Side effect:

- Does not prevent non-vertebral fractures
- DVT risk—increased
- Fatal stroke risk—increased
- Hot flushes
- Leg cramps.

V. Tissue Selective Estrogen Complex (TSEC)

The concept is partnering of a SERM with other estrogens to achieve optimal clinical results based on their blended tissue selective activity profile. The first TSEC in clinical development partners bazedoxifene (BZA), a SERM with a unique endometrial profile, with conjugated estrogens (CE).

VI. Calcitonin Nasal Spray

It reduces risk of vertebral fractures, no proven benefit for hip or non-vertebral fractures.

Other effects:

- Possible analgesic effect
- Occasional nasal irritation, rarely epistaxis
- No known drug interactions.

VII. Denosumab

It is a monoclonal antibody, specifically targets RANKL and is approved for postmenopausal women with osteoporosis at high risk of fracture. It increases both trabecular and cortical bone strength, reduces vertebral, non-vertebral and hip fracture risk. It is well-tolerated even in patients with creatinine clearance <30 ml/min.

Dose: SQ injection every 6 months.

Side effects:

- Hypocalcemia, infection, osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF) possible
- Cost
- Discontinuation:
  - Effect promptly lost
  - BMD declines
  - Effects reverse with restarting treatment.

VIII. Teriparatide

It is indicated in

- Women at high risk for fracture, including those with very low BMD (T-score worse than –3.0)
- With a previous vertebral fracture
- Those patients intolerant of or unresponsive to antiresorptive therapy
- Glucocorticoid-induced osteoporosis and male osteoporosis

Safety beyond 2 years is not known of parathyroid hormone (PTH) use.

Current recommendation is to use teriparatide in low dose 20 µg, daily, subcutaneously.

Monitor serum calcium and serum uric acid levels at 1, 6 and 12 months.

Adverse effects are headache, hypercalcemia; hypercalciuria, renal adverse effects, nausea, rhinitis, arthralgia.

Treatment options: Anabolic PTH

Benefits:

- Vertebral fracture reduction
- True anabolic effect.

Side effects:

- No non-vertebral data
- Narrow therapeutic index (18 months)
- Daily, SC injections
- Cost.

PREVENTION OF OSTEOPOROSIS

The prevention of osteoporosis begins with optimal bone growth and development in youth. Bones are living tissue, and the skeleton grows continually from birth to the end of the teenage years, reaching a maximum strength and size (peak bone mass) in children and adolescents should:

- Ensure a nutritious diet with adequate calcium intake
- Avoid protein malnutrition and under-nutrition also particularly the effects of severe weight-loss diets and eating disorders
- Maintain an adequate supply of vitamin D
- Participate in regular physical activity
- Avoid the effects of passive smoking
- Avoid heavy drinking.

It is estimated a 10% increase of peak bone mass in children reduces the risk of an osteoporotic fracture during adult life by 50%. Bone mass acquired during youth is an important determinant of the risk of osteoporotic fracture during later life. The higher the peak bone mass, the lower the risk of osteoporosis.

Once peak bone mass has been reached, it is maintained by a process called remodelling. This is a continuous process in which old bone is removed (resorption) and new bone is created (formation). The renewal of bone is responsible for bone strength throughout life.

Any factor, which causes a higher rate of bone remodelling, will ultimately lead to a more rapid loss of bone mass and more fragile bones. The nutritional and lifestyle advice for building strong bones in youth is just as applicable to adults too.

Other Treatment Options

1. Olive oil and olive polyphenols are being considered as nutritional supplements for the prevention of osteoporosis.
2. Low-magnitude whole-body vibration therapy can provide a significant improvement in reducing bone loss in the lumbar spine in postmenopausal women. Moreover, wholebody vibration can be used as an intervention for fall prevention. Eight studies were reviewed and Ma, et al. have concluded that the low-magnitude whole-body vibration therapy is an agreeable alternative for providing significant effective reduction in bone loss in the lumbar spine of postmenopausal women.
3. Research is underway regarding the relationship between chronic stress and osteoporosis. The activation of hypo-thalamo-pituitary-adrenocortical (HPA) axis leading to inhibition of gonadal hormones, and imbalance of inflammatory cytokines ultimately leading to bone loss, inhibits bone formation and stimulates bone resorption. These were the findings of Azuma, et al. and they have concluded that improvement of psychological status of women is in itself an important measure to prevent osteoporosis.
4. Many alternative medicinal methods are being studied for the purpose of prevention of osteoporosis. A recent review article has reported in detail the effects and interactions between contents of Chinese medicinal plants and various cytokines involved in bone health. The regulation of the cytokine microenvironment by immune modulation is the main common pathway. Though exact details are still being studied, they can be recommended in improving bone health with no major side effects. These form a possible basis for future research in the subject.
5. A significant role can be played by doctors of other speciality also. Orthopedicians and endocrinologists can complement the gynecologists in giving consistent advice for the postmenopausal women. In those with osteoporosis, the ill effects are compounded by falls. Prevention of falls can be helped by appropriate intervention by opthalmologists, neurologists and

cardiologists, to ensure that respective systems are working fine.

6. When it is a family physician who is attending to the patient, home visits can also be considered. The institutions which are employing women could consider taking some efforts regarding those with low physical activity. Making exercise/physical activity easy by providing for work-out rooms and the sort can be done at institutional level with good impact.

FUTURE OF OSTEOPOROSIS THERAPY

In future, treatment by stem-cell therapy may be included in the management. In 2016, researchers found that injecting a particular kind of stem cell into mice reversed osteoporosis and bone loss in a way that could, potentially, benefit humans too.

In a review by Jeffrey Kiernan, et al.

An article makes a strong case for the use of cell therapy for the treatment of human-age-related (type II) osteoporosis. The authors highlight that age-related bone loss is associated with the decline of musculoskeletal progenitors, and transplantation of such progenitors may alleviate the disease. Preclinical animal studies are integrated into the design and, as available, clinical human data into a proof of principal, that cell therapy should be explored to treat age-related bone loss. Finally, the authors make the case for the use of ancillary clinical trials to collaborate with existing human cell therapy trials to maximize the scientific impact these expensive experimental interventions.

In a review by Antebi B, Pelled G, Gazit D. DOI: 10.1007/s11914-013-0184x} *Source:* PubMed: In osteoporosis, the number of bone marrow mesenchymal stem cell (MSCs) that can differentiate into osteoblasts and form bone, is significantly reduced. In addition, recent findings suggest an imbalance in the differentiation of MSCs in favor of adipogenesis rather than osteogenesis in osteoporotic patients. The goal of stem-cell therapy is to induce bone formation via the proliferation and differentiation of bone progenitor cells. The main hurdle for stem cell-based osteoporosis therapy is the uncertainty of stem cell fate following stem cell transplantation.

Findings published in 2015 suggested that growth hormone (GH) taken with calcium and vitamin-D supplements could reduce the risk of fractures in the long term. Also in 2015, researchers in the United Kingdom (UK) found evidence that a diet containing soy protein and isoflavones may offer protection from bone loss and osteoporosis during menopause.

Scientists believe that up to 75% of a person's bone mineral density is determined by genetic factors. Researchers are investigating which genes are responsible for bone formation and loss, in the hope that this might offer new ways of preventing.

Kyphoplasty and vertibroplasty in osteoporosis: Vertebroplasty and kyphoplasty have become common surgical techniques for the treatment of vertebral compression fractures. Vertebroplasty involves the percutaneous injection of bone cement into the cancellous bone of a vertebral body with the goals of pain alleviation and preventing further loss of vertebral body height. Kyphoplasty utilizes an inflatable balloon to create a cavity for the cement with the additional potential goals of restoring height and reducing kyphosis. Vertebroplasty and kyphoplasty are effective treatment options for the reduction of pain associated with vertebral body compression fractures **(Figs 32.3 and 32.4)**.

CONCLUSION

DEXA is gold standard for BMD measurement, but needs careful assessment and clinical correlation. Detailed clinical, biochemical evaluation is important before treatment initiation. All OP patient need calcium and vitamin supplementation. Choose the drug treatment according to severity and indication.

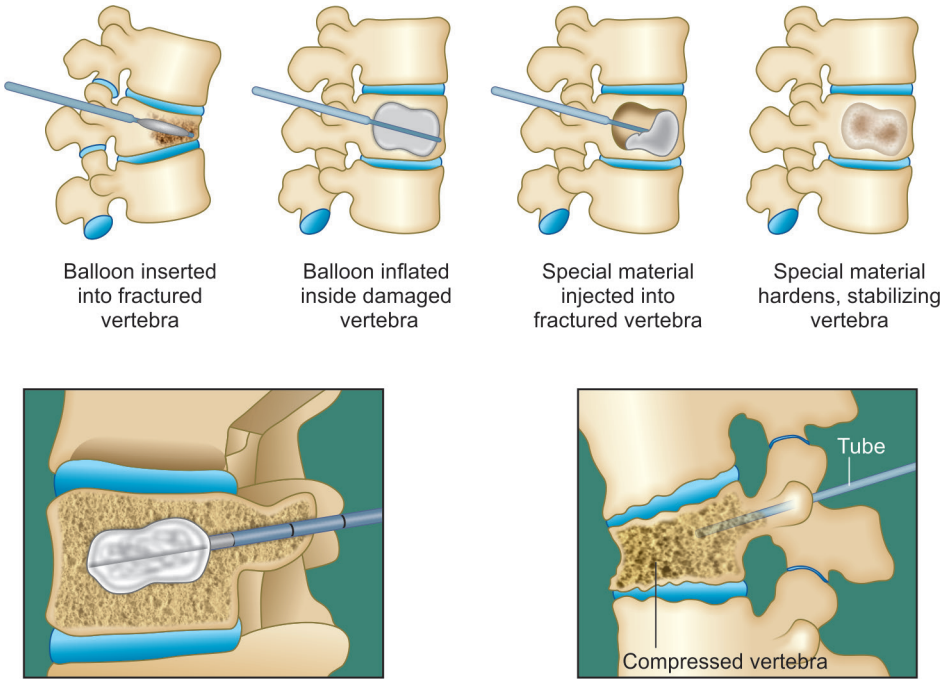


Fig. 32.3: Kyphoplasty

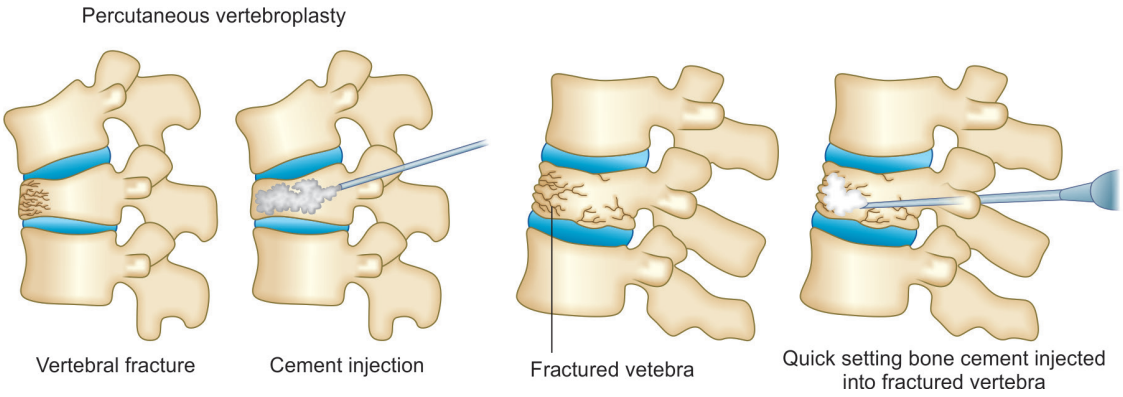


Fig. 32.4: Vertebroplasty

Osteoporosis is lifelong disease needs life-long treatment and monitoring. Attain peak bone mass. Prevent first fragility fracture or future fractures if one has already occurred.

It is never too early to start prevention of osteoporosis.

It is never too late to start treatment of osteoporosis.

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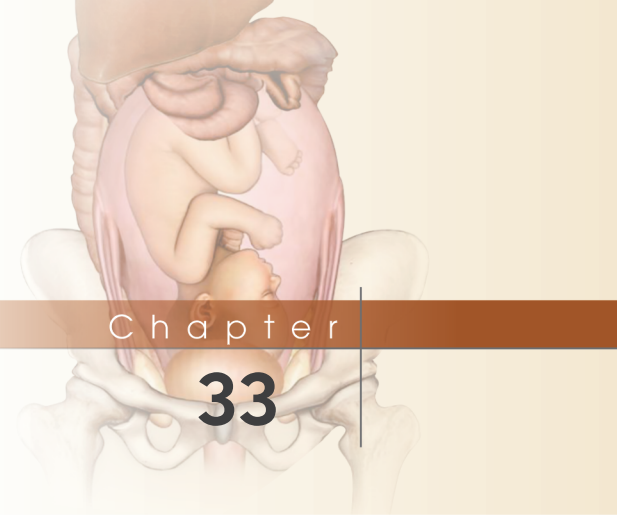


Chapter

33

Drugs in Dysmenorrhea

• Archana Bhosale • Shweta Khade

DYSMENORRHEA

The term dysmenorrhea is defined as painful menstruation of sufficient magnitude so as to incapacitate day-to-day activities.[1,2] Dysmenorrhea pain may be spasmodic (sharp pelvic cramps at the start of menstrual flow) or congestive (deep, dull ache). It is commonly associated with symptoms, such as lower backache, vomiting, headache, diarrhea and fatigue. Prevalence of dysmenorrhea can vary between 16 to 91% in women of reproductive age with severe pain observed in 2 to 29%.[3] Despite its high prevalence, there is insufficient evidence to support management-seeking practices and their perceived efficacy in females with primary dysmenorrhea.

TYPES OF DYSMENORRHEA

1. Primary Dysmenorrhea

Dysmenorrhea occurs in absence of pelvic pathology. It is more common in adolescents and young adult females and usually starts 1 to 2 days before the onset of menses or just after the menses with pain, typically lasting for 1 to 3 days. It may be associated with systemic, gastrointestinal and psychological symptoms. The systemic symptoms include headache, lethargy, fatigue, sleepiness/sleeplessness, tender breasts, heavy lower abdomen, backache, painful knees and inner thighs, myalgia, arthralgia, and swollen legs, sweating. The gastrointestinal symptoms include an increase or decrease in appetite, nausea, vomiting, and bloating, constipation, diarrhea. Psychological symptoms include anxiety, depression, irritability, and nervousness.[4]

Pathophysiology: In ovulatory cycles, during menses endometrial sloughing causes endometrial cells to release prostaglandins (PGs) $PGF_{2\alpha}$, PGE_2, vasopressin and leukotrienes, which stimulates myometrial contractions and ischemia. Depending upon the levels of prostaglandin release, the degree of dysmenorrhea varies. The secretion of prostaglandins causes uterine contractions along with other ailments, such as nausea, vomiting, headache and tympanites.[5,6]

2. Secondary Dysmenorrhea

It is defined as painful menstruation due to pelvic pathology or recognised medical condition. It is associated with diffused or constant pain that does not necessarily occur during menstruation.[5] It is usually detected in females with age more than 24 years with no history of dysmenorrhea. They have clinical features that distinguish their condition from primary dysmenorrhea, which includes a large uterus, pain during sexual intercourse, and resistance to effective treatment.

ASSOCIATED RISK FACTORS[7]

Various risk factors are associated with it and enlisted below.

1. Age (13 to 15 years)
2. Smoking
3. Attempts to lose weight
4. Body mass index (BMI) (less than 17 and more than 30)
5. Depression or anxiety
6. Earlier age at menarche
7. Nulliparity
8. Longer and heavier menstrual flow
9. Family history of dysmenorrhea
10. Disruption of social network.

TREATMENT OF DYSMENORRHEA

Treatment of dysmenorrhea depends on the type and severity of dysmenorrhea. In this chapter, we will discuss case-based medical management approach to treat dysmenorrhea.

Initial approach: Detailed patient history and clinical examination should be done to rule out pelvic pathology at the first visit. Patients should be educated regarding menstrual cycles, causes and symptoms of dysmenorrhea and reassurance should be given. Treatment is planned according to age and symptoms.

Non-pharmacological interventions: Pain relief without medication is an important healthcare target and it is safe and inexpensive and easily accepted by patients.

Acupuncture, heat therapy, psychotherapy, massage therapy, hypnotherapy, physiotherapy, transcutaneous electrical nerve stimulation (TENS) are used to reduce the primary dysmenorrhea immensity.

Mechanisms

Increasing pelvic blood supply, inhibiting uterine contractions, release of endorphins and serotonin, and altering the ability to receive and perceive pain signs.[8]

PRIMARY DYSMENORRHEA: PHARMACOLOGICAL MANAGEMENT (CASES 1 TO 9)

Indications: Patients who do not have adequate relief with non-pharmacological interventions or who desire immediate pharmacologic therapy.

Case 1: Adolescent Girl (10 years to 18 years) with Dysmenorrhea

Most adolescent girls will have primary dysmenorrhea and will respond well to empirical treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and antispasmodics **(Table 33.1)** or progesterone oral hormonal preparation **(Table 33.2)** or both. Progesterone preparation in the form of norethisterone acetate or medroxyprogesterone acetate 5 to 10 mg daily to be used.

Dose schedule should be individualized depending upon age and symptoms. A short protocol for the last 10 days before menses or cyclical 21 days regimen can be used. Duration of treatment will be 6 to 9 months. Resistant cases can be evaluated by ultrasonography to rule out pelvic pathology.

Medical management:

1. *NSAIDs and antispasmodics:* These drugs are used as the first line of management of dysmenorrhea. It should be started 1 or 2 days prior to menses and to be continued for initial 2–3 days of menses along with antacids. Antispasmodics to be started with initiation of symptoms and can be given for 3–5 days. NSAIDs and antispasmodics which can be used safely in adolescent girls are discussed in detail in **Table 33.1**.
2. *Hormonal management:* Progesterone preparations (oral formulations)—patients whose dysmenorrhea is not curable by NSAIDs could be given hormone therapy for at least three menstrual cycles. About 75% of patients receiving progestins experience reduction in pain. Combined estrogen–progesterone pills and depot

Table 33.1: NSAIDs and antispasmodics[9]

Drugs	*Mechanism of action*	*Dosages*	*Max. dose*	*Side effect*	*Contraindications*
A. NSAIDs					
1. Paracetamol (para-aminophenol)	Inhibition of two isoforms of cyclo-oxygenase, COX-1 and COX-2, which are involved in prostaglandin (PG) synthesis	325 mg to 1 g orally every 4 to 6 hours	4 g per 24 hours	Nausea, vomiting, constipation, hypersensitivity rash, pruritus, hepatotoxicity	Hypersensitivity to acetaminophen, severe hepatic impairment, or severe active hepatic disease
2. Ibuprofen (propionic acid derivative)	Non-selective inhibitor of cyclo-oxygenase COX-1 and COX-2	200 to 400 mg orally every 4 hours as needed	3200 mg/day	Gastritis, ulceration, hemorrhage, perforation, diminished renal function, rashes	Active GI or cerebrovascular bleeding, uncontrolled heart failure, lupus, renal impairment, and hepatic impairment
3. Mefenamic acid (anthranilic acid derivative)	Inhibitor of COX-1 and COX-2	250 mg orally every 6 hours as needed	Not to exceed 3 days	• Diarrhea • Nausea, stomach bloating • Swelling of the face, fingers • Feet, • Lower legs	History of asthma, urticaria, or other allergic-type reactions after aspirin or other NSAIDs
4. Naproxen (propionic acid derivative)	Blocks arachidonic acid to inhibit COX-1 and COX-2	275 mg every 6 to 8 hourly	1100 mg/day	GI intolerance	Hypersensitivity, liver and renal impairments
B. Antispasmodics					
Drotaverine (smooth muscle relaxant)	Selective inhibitor of phospho-diesterase-4	80 mg every 12 hourly	240 mg/day	Heating sensation, dizziness, headache (rarely), insomnia	Liver and kidney failure and in severe heart failure and in children under 12 years of age
Hyoscine butyl bromide (antimuscarinic)	Anticholinergic action—binds to muscarinic acetylcholine receptors, blocking their effect	2 tablets (40 mg), taken 4 times a day	160 mg/day	Side effects may include sleepiness, vision changes, dry mouth, rapid heart rate, triggering of glaucoma, and severe allergies	Myasthenia gravis, mechanical stenosis in the gastrointestinal tract, paralytical or obstructive ileus, megacolon

(*Contd...*)

Table 33.1: NSAIDs and antispasmodics[9] (*Contd...*)

Drugs	*Mechanism of action*	*Dosages*	*Max. dose*	*Side effect*	*Contraindications*
Dicyclomine + Paracetamol (antimuscarinic)	Dicyclomine is a muscarinic M1, M3, and M2 receptor antagonist as well as a non-competitive inhibitor of histamine and bradykinin	325 to 650 mg every 4 to 6 hours	4 g per day	Liver damage or allergic reactions like swelling of the mouth, face, throat, difficulty in breathing, skin rash, or itching	Hypersensitivity to acetaminophen, severe hepatic impairment, or severe active hepatic disease
Camylofin + Paracetamol	Camylofin is a smooth muscle relaxant with both anticholinergic action	25 mg camylofin + 300 mg PCM	4 g per 24 hours	Skin rash, headache, granulocytopenia, irregular heart rate	Heart disease, glaucoma (narrow angle)

medroxyprogesterme acetate (DMPA) use has been associated with smaller gains or loss of bone mass during this critical age period for acquiring bone strength, therefore should be averted. Oral progestin formulations are enlisted in **Table 33.2**.

Case 2: Young Unmarried Female (Age ≥18 years) with Dysmenorrhea

Detailed history, clinical examination, pelvic ultrasonography and if required magnetic resonance imaging (MRI) is to be done. Drugs of choice will be NSAIDs and antispasmodics **(Table 33.1)** or hormonal suppression or both. Progestin **(Table 33.2)** or combinations of estrogen and progesterone (low dose or high dose) can be used depending upon ultrasonography (USG) findings. Duration of treatment will be 6 to 9 months. If there is any pelvic pathology, then treatment is based on the type of pelvic pathology.

Hormonal management (oral formulations): Progestin preparations or combined estrogen–progesterone—patients not responding to NSAIDs, start with hormone therapy for at least three menstrual cycles. Continuous

Table 33.2: Progestin preparations (oral formulations)[10]

Progestin preparation (oral)	*Mechanism*	*Oral dosage*	*Side effects*
Medroxyprogesterone acetate (pregnanes), C-21 progestin	Decidualization and atrophy of endometrium	5 or 10 mg daily for 5 to 10 days starting on day 16 or daily for 21days (cyclical)	• Irregular bleeding/ spotting • Mood variability • Depression • Bloating • Breast tenderness • Weight gain • Drowsiness
Norethindrone acetate (estrane) 19-nor-testosterone		5 or 10 mg daily for 5 to 10 days starting on day 16 or daily for 21days (cyclical)	
Dydrogesterone (gonanes) 19-nor-testosterone		10–30 mg twice/ thrice daily for 6 months	

combined oral pills for 3 months give excellent results.

Case 3: Married Female with Dysmenorrhea Desiring for Contraception

After evaluation, if there is no pelvic pathology, different hormonal preparations can be used in the form of oral, injectable, implants, patches, vaginal rings, intrauterine devices. It should be started on day 1–3 of menses and continues for 21 days for 6 to 9 months or as long as contraception is required.

Apart from oral preparation injectables, vaginal rings, transdermal patches and intrauterine devices are widely available and can also be used safely in these women. Various available formulations of combined estrogen–progesterone and progestin are enlisted in **Table 33.3**.

Table 33.3: Hormonal preparation: Combined estrogen–progesterone and progestin[11]

Hormonal preparation	*Formulations*	*Dosage*	*Side effects*	*Contraindications*
Combined (estrogen + progesterone) Mechanism of action: 1. Synthetic progestins suppress ovulation and make the endometrium thin which has small amounts of arachidonic acid, the substrate for most prostaglandin synthesis. 2. It reduces both uterine bleeding flow and contractions during menses, which decreases dysmenorrhea.	1. OC pills: Low/ high dose	Ethinyl estradiol (20 or 30 µg) + LNG (0.15 mg)	Nausea vomiting, weight gain, venous thrombosis mastalgia	Arterial venous thrombosis severe hypertension, DM with vascular complications, active liver diseases breast cancers
	2. Transdermal patch	Ethinyl estradiol (20 µg) + Norelgestromin (0.15 mg)		
	3. Vaginal ring	Ethinyl estradiol (15 µg) + Etonogestrel (0.12 mg)		
Progestin mechanism Progestins cause endometrial atrophy and inhibit ovulation	Oral progestin	Refer **Table 33.2**		
	DMPA: Depot intramuscular	Medroxyprogesterone acetate 150 mg every 3 monthly	Irregular menses, amenorrhea, loss of BMD	Unexplained vaginal bleeding, thromboembolic diseases, breast cancer, osteoporosis
	LNG (IUD): Intrauterine device	Levonorgestrel, 52 mg (20 µg/day)	Irregular frequent menses, spotting	
	Norplant	Etonogestrel, 68 mg	Acne, mastalgia, menstrual irregularities	

Table 33.4: GnRH agonists and antagonists[13]

Preparation	*Mechanism of action*	*Dosages*	*Side effect*
GnRH agonist	Prolonged activation of GnRH receptors by GnRH leads to desensitization and consequently to suppressed gonadotrophin secretion		Menopause-like side effects, high cost, loss of bone density with long-term use
1. Nafarelin		200 µg intranasal spray twice day	
2. Leuprolide acetate depot		3.75 mg intramuscularly every 4 weeks	
GnRH antagonist	It competes with GnRH for receptors on gonadotroph cell membranes, inhibits GnRH-induced signal transduction and consequently gonadotrophin secretion	Tab 150–200 mg, OD for 6 months	Hot flushes, night sweat, nausea, weight gain, vomiting
1. Elagolix			

Case 4: Patients with Continued Menstrual Pain Despite NSAIDs and Hormonal Treatment

Reassess patients by clinical examination and USG to rule out pelvic pathology. Minimally invasive techniques, such as transcutaneous electrical nerve stimulation can be offered to patients who still insist on conservative management.[12]

1. Transcutaneous electrical nerve stimulation: Percutaneous tibial nerve stimulation (PTNS).

Mechanism:

1. It raises the threshold for pain signals from uterine hypoxia and hypercontractility by sending a volley of afferent impulses through the large diameter sensory fibers of the same nerve root, resulting in lower perception of painful uterine signals.
2. Peripheral nerves and the spinal cord release endorphins.[8] The major limitation need for continuous treatment for 12 weeks.

Role of laparoscopy: In absence of pelvic pathology diagnostic laparoscopy can be offered. The most common diagnosis is endometriosis as mild grade of endometriosis can not be detected by USG.

Case 5: Patients with Persistent Dysmenorrhea who Desire to Avoid Surgery (Diagnostic Laparoscopy)

Empirical treatment with a gonadotropin hormone-releasing hormone (GnRH) agonist analog or antagonist: Make an endometriosis presumptive diagnosis and suggest empirical GnRH agonist or antagonist therapy. With either agonist or antagonist medication, if the pain significantly diminishes or goes away, endometriosis is likely present, however this is not proven. Details of GnRH agonist or antagonist are given in **Table 33.4**.

Case 6: Patients with Persistent Pain and Negative Laparoscopy

If laparoscopy is negative and the patient has previously failed both hormonal contraception and NSAIDs, a 3-month course of a GnRH agonist analog can be tried, since endometriosis may have been missed. Even in the hands of experienced laparoscopists, an accurate diagnosis of endometriosis can be difficult, since the disease is often microscopic and presents visually with a variety of atypical lesions. Calcium supplementation 1–2 g daily should be considered with GnRH agonist.

Refractory dysmenorrhea: (Cases 7, 8, 9). Despite the above treatments, a minority of patients will continue to have dysmenorrhea that limits their function. Treatment options for refractory dysmenorrhea should be individualized as per age and future childbearing. Cases 7, 8 and 9 are discussed as follows:

Case 7: Patient with Abnormal Uterine Bleeding with Dysmenorrhea

Patients who do not desire future childbearing but want to retain uterus—endometrial ablation can be advised.

Case 8: Patients who have Exhausted All Treatment Options and have Completed their Childbearing

Hysterectomy is the definitive treatment.

Case 9: Patients with Chronic Midline Pelvic Pain with no Organic Pathology

Nerve transection procedures like pre-sacral neurectomy can be done.

Non-pharmacological Supportive Treatment[14]

- *Exercise:* It functions by enhancing pelvic blood flow and triggering the production of endorphins, which serve to reduce pain. Increasing physical activity is a sensible strategy to lessen dysmenorrhea due to its numerous health advantages and a low risk of injury. Walking, yoga, and cardiovascular exercises should be done for 30 to 45 minutes.
- Apply heat pack to the lower abdomen. It can increase circulation, ease muscle tension, and relax the abdominal muscles to lessen pain brought on by muscle spasms. The effectiveness of other treatments may be increased by heat therapy.
- Behavioral counseling changes how they perceive their pain (such as desensitization-based techniques, hypnotherapy, imagery, and coping mechanisms) and how they react to pain (*e.g.* biofeedback, electromyographic training, exercises, relaxation training). In motivated patients, it serves as an adjuvant to therapeutic exercise and medication.

Complementary Medicine[15]

- Acupuncture or acupressure—improvements were noted in the worst pain intensity, number of days with pain, and proportion of patients using pain medication.
- Diet and vitamins—dietary advice to avoid food that causes bloating and water retention, *e.g.* fatty foods, carbonated beverages, caffeine and salty foods. A variety of dietary changes and vitamin therapies has been reported to reduce the severity of menstrual pain, which includes
  1. Low-fat vegetarian diet
  2. Increased dairy intake
  3. Vitamin E (500 units per day or 200 units twice per day, beginning 2 days before menses and continuing through the first three days of bleeding)
  4. Vitamin B_1 (100 mg daily), vitamin B_6 (200 mg daily), and fish oil supplement, vitamin D_3
  5. Ginger powder consumption: 750 to 2000 mg of on days 1 to 3 of the menstrual cycle
  6. Chinese herbs.

Unproven Treatment[16]

- *Nerve transection procedures:* Laparoscopic uterosacral nerve ablation (LUNA), pre-sacral neurectomy (PSN) involve transection of (uterosacral ligaments or pelvis) afferent nerve fibers causing interruption of cervical sensory pain fibers in patients with chronic midline pelvic pain associated with endometriosis.
- *Tocolytics:* Nitric oxide, calcium channel blockers and nitroglycerin all have tocolytic effects and are under investigation as potential therapies of dysmenorrhea.
- *Magnesium:* Phosphodiesterase inhibitors—by inhibiting phosphodiesterase, sildenafil

Table 33.5: Causes of secondary dysmenorrhea

Causes of secondary dysmenorrhea	*Signs: Dysmenorrhea with*	*Diagnosis*	*Management*
Gynecological causes			
Endometriosis	dyspareunia, infertility	Clinical examination/ USG/laparoscopy	Medical/surgical/ combined
Adenomyosis	Abnormal uterine bleeding	Clinical examination/ USG/MRI	Medical/surgical/ combined
Fibroid	Large uterus	Clinical examination/USG	Medical/ surgical
Endometrial polyp	Abnormal uterine bleeding	Clinical examination/ USG/ hysteroscopy	Polypectomy
Pelvic inflammatory syndrome	Vaginal discharge	Clinical examination/USG	Antibiotics and anti-inflammatory drugs
Obstructive mullerian anomalies	Large uterus	Clinical examination/ USG/MRI/laparoscopy	surgery
Use of IUCD	Non-cyclical pain	Clinical examination/USG	NSAIDs/ removal
Pelvic congestion syndrome	Non-cyclical pain	USG/Doppler	NSAIDs
Other causes			
Gastro-intestinal: Inflammatory and irritable bowel syndrome	Constipation/diarrhea	USG/gastrointestinal endoscopy	Medical
Renal: Ureteropelvic obstruction	Loin-to-groin pain	USG/CT scan	Medical/surgical
Psychogenic	Pain at multiple site	Detailed history by specialist	Counseling/medical

enhances the vasodilatory effects of nitric oxide, facilitating myometrial blood flow, and thus reducing primary dysmenorrhea.

SECONDARY DYSMENORRHEA

It is defined as dysmenorrhea due to pelvic pathology. Along with accompanying pelvic disease, prostaglandin release and anatomical mechanisms are also responsible for secondary dysmenorrhea. Various causes of secondary dysmenorrhea, their diagnosis and management are discussed in Table 33.5.

Gynecological pathologies: Most common pelvic pathologies which are associated with secondary dysmenorrhea are discussed below.

1. Endometriosis: Among the various gynecological pathologies endometriosis is the commonest benign disorder defined as the presence of functional endometrium outside the uterine mucosa. It is seen in around 8–10% of reproductive age group females, affecting 20–50% infertile population and chronic pain (3–80%). It is usually diagnosed based on symptoms/ physical examination and confirmed on ultrasonography or laparoscopy, but finally proven by histopathology of the specimen.

2. Fibroid uterus: It is the second most common pelvic pathology. Fibroids vary in number, size and location. It gives rise to different types of pain patterns, like dull

to sharp pain, menstrual cramping pelvic pain, low back pain, abdominal pressure, dyspareunia, rectal and bladder pressure (uncomfortable pressure leads to pain). It can also compress sciatic nerves leading to leg pain. Causes of acute pain in the abdomen are twisted pedunculated fibroid, submucosal fibroid and red degeneration of fibroid. Posterior fibroids may cause low backache and anterior fibroid can contribute to anterior pelvic pain, pressure and urinary complications.

3. Pelvic inflammatory disease (PID): It involves infection and inflammation of the upper genital tract including uterus, cervix, ovary and fallopian tube. Outpatient and inpatient management depends upon severity of disease. Patients may complain of continuous dull aching lower abdomen pain with or without fever.oral or parenteral antibiotics are required to treat this condition. For chronic pelvic pain the possibility of tuberculosis should be ruled out.

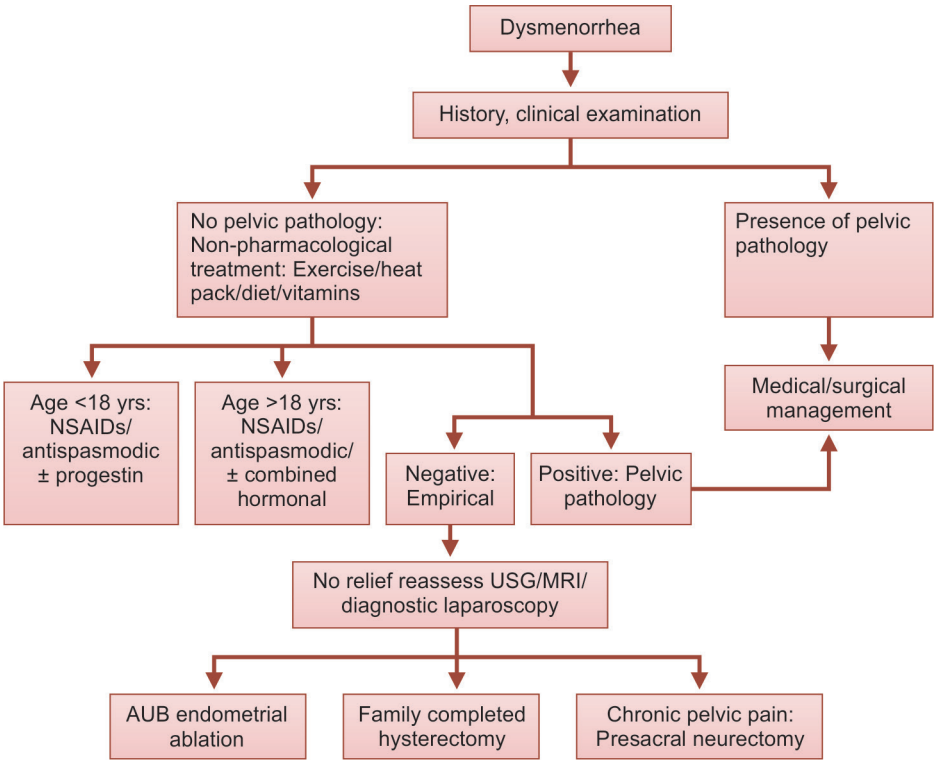
Treatment for Secondary Dysmenorrhea

It varies depending upon type of pelvic pathology, age of patient, severity of symptoms and child bearing status. For

Table 33.6: Medical management for secondary dysmenorrhea[17,18]

Gynecological pathology	*Drugs used*	*Mechanism of action*	*Dosages*	*Side effects*
Endometriosis/ adenomyosis	Dienogest	Atrophy of endometrium	2 mg one or twice a day for 3 to 6 months	Irregular bleeding spotting Mood variability
	Androgens: 1. Danazol 2. Gestrinone	Inhibits steroidogenesis and atrophy of lesion	400–800 mg, orally in 4 divided doses for 6–9 months 1.25/2.5 mg, twice a week for 6–9 months	Acne, hirsutism, voice changes, diminished breast size, decreased libido
	Progesterone (NEW) Drospirenone	Decidualization of endometrium	4 mg, once a day for 21 days for 3 cycles	
	Aromatase inhibitor: 1. Letrozole 2. Anastrozole	Reduces estrogen synthesis with lesion atrophy	2.5 mg daily for 6 months 1 mg daily for 6 months	Headache, nausea, vomiting, skin changes, vasomotor symptoms, arthralgia, osteoporosis
	SERMs: 1. Tamoxifen 2. Raloxifene	Inhibit estrogen receptors	40–60 mg/day for 6 months	Fatigue, hot flushes, night sweats, vaginal discharge, mood swings
Fibroid	SPRMs: 1. Ulipristal 2. Mifepristone	Antiproliferative effects in the endometrium	5 mg /day for 6 months 25 mg/day for 3 months	Dizziness, hot flushes, fatigue, headache, nausea, vomiting
PID	Antibiotics and anti-inflammatory drugs	Cap. doxycycline Tab. metronidazole	100 mg, BD, for 14 days 400 mg, TDS, for 7 days	Nausea vomiting

Flowchart 33.1: Management of dysmenorrhea



mild-to-moderate grades of above mentioned pathology medical management is preferred whereas moderate to severe grades of pelvic pathologies may require surgical interventions. Table 33.6 enlists different drugs used in various pelvic pathologies.

Treatment management of dysmenorrhea is shown in Flowchart 33.1.

CONCLUSION

Due to the vast range of physical and psychological symptoms, dysmenorrhea has a detrimental impact on quality of life and decreases attendance at work and school. The primary focus of treatment for this illness is pain reduction, whether achieved pharmaceutically or through the use of complementary therapies. Treatment should be individualized depending upon age of patient and severity of symptoms.

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Chapter

34

Drugs in Fibroids

• Rajeshwari L Khyade • Madhuri Patel • Aaishwarya R

Introduction

Uterine leiomyomas better known as uterine fibroids, are most frequent nonmalignant smooth muscle tumors of the uterus.

They are the most common tumors found in the female reproductive system.

Uterine fibroids are common in 50–60% of women.

Most are asymptomatic.

Patients with asymptomatic uterine fibroids and who do not desire of pregnancy do not need any intervention except for serial ultrasonography (USG) monitoring for the growth of fibroid and their condition.

In 30–40% of cases, fibroids cause morbidity due to abnormal uterine bleeding and pelvic pressure.

This disease is one of the major concern of health expenditure in gynecology field African–American women have a greater chance of being affected by uterine fibroids,[1] due to high follicle-stimulating hormone (FSH).

Uterine fibroids can occur at any time between menarche and menopause but are mostly seen in 35–49 years of age.

They typically resolve after menopause.

Pathogenesis of fibroids is still unclear, however they are estrogen and progesterone dependent tumors.

Diagnosis is usually either by pelvic ultrasound with Doppler studies or by magnetic resonance imaging (MRI).

MRI is preferred because of its greater ability to demonstrate individual fibroids and for fibroid mapping, *i.e.* denote their size, location, and number within the uterus.[2–5]

The definitive treatment, so far, has been hysterectomy and sums up to two-thirds of all hysterectomies done in premenopausal women.

Myomectomy is an option for patients desiring child-bearing and in women who want to preserve her uterus.

Uterine artery embolization also is a form of conservative management of myomas, but carries risk of premature ovarian failure and has its own risks, limitations, and availability is an issue.

Medical treatment is given to:

1. Reduce the symptoms
2. Preoperatively
3. Correction of anemia
4. Shrinkage of fibroids
5. To preserve fertility
6. To avoid or delay surgery.

After evaluating 52 studies came to a conclusion that proves the efficacy of a number of agents, as medical alternative to surgery.[6,7]

The drugs most commonly used are:

1. Gonadotropin-releasing hormone (GnRH) agonist and antagonist
2. Selective progesterone receptor modulator (SPRM)
3. Progestogens.

GnRH agonist reduces leiomyoma size to about 50% in 3 months, but it is expensive and has to be given parenteral.

Long-term use of GnRH agonists treatment is accompanied by side effects, such as hot flushes, night sweats, bone resorption due to hypoestrogenic effect, etc. and the need for add back therapy. Cessation of GnRH causes regrowth of myoma and recurrence of symptoms; therefore use of GnRH is limited for only 6 months or prior to surgery.

GnRH agonist-produced side effect is overcome with the use of GnRH antagonist cetrorelix.

A new kid on the block, in its earlier phase is orally-active nonpeptitide GnRH-receptor blocker, elagolix.

The levonorgestrel intrauterine device (LNG-IUS) is effective in decreasing menstrual blood loss, correcting hemoglobin levels, and it can be an alternative to surgical treatment.

Although the expulsion rate of levonorgestrel intrauterine device is high in patients with fibroid uterus.

When the cavity is big, it is ineffective of the SPRM, ulipristal and mifepristone.

Ulipristal is an expensive option and should be used with caution because of rare occurrence of liver complications.

Mifepristone is effective in reducing the size of fibroid and is a more cost efficient.

All SPRMs produce unique endometrial changes that are benign, reversible and have negative consequences.

Progestogens

Progestogens produce results similar to natural hormone progesterone in the body, used in medical management of fibroids. They include progesterones made from plant and synthetic form, that is bio-identical progesterone. Progesterone was first used in 1940 to manage fibroids.

Depot medroxyprogestrone acetate (DMPA) inj., intramuscularly, to treat and prevent increase in the size of fibroids.

LNG–IUD-containing levonorgestrol, 52 mg, releases daily 20 μg, acts locally thereby causing thinning of the endometrium and decreases the menstrual blood flow.

It can be safely used for 5 years.

As progestogens temporarily reduce the bleeding, cannot be used for long-term medical therapy.

They exert dual action on myomas. Moravek, et al. concluded that progesterone and progestin play a key role in uterine fibroid growth, hence it is like adding fuel to the fire.

Estrogen–progestin combinations (oral contraceptives), especially low dose estrogen:

1. Decreases menstrual pain,
2. Decreases length and severity of bleeding
3. Regulates menstrual bleeding and
4. Does not cause the growth of new fibroids.
5. They may have beneficial effect on the size of already existing fibroids.

In May 2021, United States Food and Drug Administration approved estradiol and norethindrone acetate (MYFEMBREE®) for the treatment of symptomatic fibroids for duration of 2 years in a perimenopausal women.

This changed the dynamics of treatment of fibroids, as there were very few noninvasive methods.

Selective Progesterone Receptor Modulators (SPRMs)

SPRM are providing a great hope and change as an effective medical therapy for fibroids with fewer side effects and beneficial long-term effects.

Mifepristone and Ulipristal Acetate

Mifepristone: Synthetic steroid, code name RU 486, is the first SPRM to be produced and used clinically.

It is antiestrogen hormone, weak antiprogestin, which antagonizes progesterone receptors.

Though estrogen is major contributor for fibroids, many studies show the effect of progesterone, which promotes fibroid cell mitosis, and thus fibroids grow.

MIFEPRISTONE

It causes:

1. Heavy menstrual bleeding
2. Reduction in fibroid size
3. Pain
4. Improves overall the quality of life.

Mechanism of Action

Low-dose progesterone blocks by competitively binding its intracellular receptors.

They inhibit progesterone receptor (PR) and EGF mRNA gene expression in the myoma, which are overexpressed in myomas.

Glutathione pathway also was significantly changed, thus causing inhibitory effect on the growth of fibroids.

Pharmacokinetics

Mifepristone is active orally.

- Bioavailability is only 25%.
- It is largely metabolized in the liver by CYP3A4.
- Excreted in bile.
- $t_{1/2}$ is 20–36 hours.

  Some enterohepatic circulations occur.

Side effects: Causes endometrial hyperplasia.

Dosage

5–10 mg, 25 to 50 mg, daily, once, orally for 3–6 months.

Many domestic and international clinical studies.

Have show the effect of mifepristone.

- When given for 3 months in doses of 10, 25 and 50 mg.
- Decreased the size of uterine fibroids and uterine volume.

To obtain amenorrhea, decreased clinical symptoms, controlled bleeding and corrected anemia.

It even cut short the surgical time, amount of bleeding and the need for blood transfusion if surgery was considered later.

Clinical Approach

Contraindication: Ectopic pregnancy, hypersensitive to prostaglandin, undiagnosed renal masses, concurrent intrauterine device (IUD) causes allergic disorders and anemia.

Side effects: Leg cramps, hot flushes, Abdominal cramping, allergic reaction, diarrhea, dizziness, fainting, fatigue, headache, insomnia, indigestion, nausea and vomiting.

Neelofer Shaikh, et al.[8] compared the efficacy of using 25 mg daily and 50 mg twice weekly for 3 month, the results were mifepristone in both dosages is highly efficacious in causing amenorrhea, improving anemia, and enhancing the quality-of-life, and hence 50 mg biweekly dosage shows potential for being cost efficient.

Another study by Vidushikulshresthra[9] dose of 10 versus 25 mg, given daily for 3 months, there was greater reduction of myoma size with 25 mg dose, amenorrhea was seen in 90–95% of patients, which is reversible. Symptomatic relief with more than 90% reduction in menstrual blood.

Gil Yerushalmi, et al.[10] did study to evaluate the efficacy and safety of vaginal mifepristone, 10 mg, daily for 3 months treatment on uterine leiomyoma and related symptoms. The results were similar to other studies given orally. There were no major side effects and improved the quality-of-life. There was no evidence of endometrial hyperplasia or atypia.

GnRH AGONIST

Short peptide analogues of GnRH cause profound down regulation of pituitary, which cause inhibition of estrogen and androgen synthesis.

Leuprolide, goserelin and triptorelin are GnRH agonist.

Mechanism of Action

GnRH is a decapeptide, synthesized in the hypothalamus.

Reaches GnRH receptor of gonadotropin cells in the pituitary gland, triggers a domino effect.

Stimulates the release of luteinizing hormone (LH) and follicular-stimulating hormone (FSH), which results in the production and release of estrogen by the ovaries, that is stimulates hypothalamic pituitary ovarian axis.

As fibroids are estrogen and progesterone-dependent GnRH causes growth of fibroids.

GnRH is typically produced in a small rhythmic burst pulsatile manner, GnRH agonist changes the pattern of GnRH release.

GnRH agonists when administered cause an initial flare effect, increasing in sex hormones, but with continued constant flow in a non-pulsatile stimulation, LH and FSH, estrogen and progesterone synthesis is halted and ovulation declines.

Thus, prolonged activation of GnRH receptors by GnRH leads to desensitization and suppression of gonadotropin secretion,

Without estrogen, menstruation stops.

Hypo-estrogenic state causes fibroids to regress in size and decreasing its fibroid-associated symptoms.

Finally, GnRHa directly acts on myomatous cell inducing a suppression of cell proliferation and apoptosis.

GnRH analogues are more potent and sustained in action.

The native decapeptide have been used extensively in modulation of sex hormone synthesis.[11]

The advantages of the preoperative use of gonadotropin-releasing hormone agonists are:

1. Reduction in uterine and myoma size
2. Vascularity
3. Correction of anemia
4. Potentially improved operative technique
5. Uterine cavity integrity and
6. Abdominal hysterectomies could be converted to vaginal hysterectomies
7. Fewer post-operative complications.[12]

Fibroid shrinkage occurs in the initial 8–10 weeks, highest after 14 weeks of treatment, after this, steady state of reduction occurs.

Efficacy of the drug is 90%. And is a suitable alternative to surgical intervention.

Efficacy is higher in women under 35 years.

Women with the largest initial uterine or fibroid volume were more likely to undergo the greatest fibroid shrinkage.

The lower the serum estradiol levels the greater the tumor shrinkage.[13]

Gonadotropin-releasing hormone analogues are very effective in reversing heavy menstrual bleeding and pain.

The fibroids regrow quickly about 6 months once medication is discontinued,

As effects are temporary.

GnRHa treatment are not recommended for long time because of

1. Potential side effects
2. Complications
3. High cost
4. Need for add-back therapy.

The course of GnRHa should be used:

1. Long-term protocol for 6 months in pre-menopausal women to induce iatrogenic climacteric stage and in those waiting to attain menopause, later shrinks on its own.
2. Short-term for 2–3 months, preoperatively, prior to surgery.
3. Intermittent 6-month course is effective in treating myoma symptoms to limit climacteric like state.

Use of GnRHa for more 6 months warrants add-back therapy.

Drugs used for add-back therapy are:

1. Progestin—MPA, 20 mg/day
2. OC pills.
3. Tibolone—2.5 mg/day
4. Ipriflavone—reduced bone loss
5. Raloxifine—60 mg daily in postmenopausal women.

Pre-surgical GnRHa use indicates a definite treatment advantage and the use of GnRHa as adjuncts to surgery are well-established.[14]

Pharmacokinetics

GnRH agonists are derived from native GnRH, by substituting a D-amino acid for the native L-amino acid position 6 of the native decapeptide.

This substitution makes the agonist resistant to degradation by endopeptidases, resulting in prolonged receptor occupancy.[15]

Leuprorelin acetate is a synthetic non-apeptide agonist analogue of gonadotropin-releasing hormone.

Continued leuprorelin administration causes medical castration.

As leuprorelin is a nonapeptide, is orally inactive and given subcutaneously or intramuscularly, nasal spray.

The hydrophilic leuprorelin is entrapped in biodegradable highly lipophilic synthetic polymer microspheres.

The peptide drug is released from these depot formulations at a constant daily rate for 4–12 weeks to avoid daily injections.

With doses ranging between 3.75 and 30 mg.[16]

Onset of action: Initial transient flare, hormone suppression occurs 2–4 weeks of continued therapy.

- Protein binding: 43–49%
- Metabolism: It is metabolized to smaller inactive peptides that are further catabolized.
- Bioavailability: 94%
- Half-life elimination: ~3 hours
- Excretion: Urine.

Side Effects

- Stops production of estrogen and progesterone
- Hot flushes, mood changes
- Vaginal dryness, lower sex drive
- Transient frontal headache
- Arthralgia, myalgia, insomnia, edema, emotional liability, depression and decreased libido.
- Hypo-estrogenic state induced by GnRH causes significant bone loss and osteoporosis after 6 months of therapy.
- Therefore, they will require add-back therapy with oral contraceptive (OC) pills or progestin to help mitigate the side effects of bone loss and hot flushes.
- Dosage-related long-term metabolic abnormalities are like weight gain, worsening of diabetic and osteoporosis.

Uses of Various Drugs

Clinical approach: Used in endometriosis, precocious puberty, infertility and uterine fibroid and other sex hormone-related disorders.

ULIPRISTAL ACETATE

Ulipristal acetate known as CDB-2914, is a synthetic orally active SPRM, characterized by a tissue-specific partial progesterone antagonist effect.[17]

Mechanism of Action

It reversibly blocks the progesterone receptors.

1. Hypothalamus,
2. Uterus,
3. Cervix
4. Ovaries.

UPA, as a progesterone antagonist:

1. Prevents the proliferation of leiomyoma cells
2. Initiates apoptosis
3. Increases cleaved caspase-3 expression
4. Reducing Bcl-2 expression.[18]

5. Downregulates the expression of angiogenic growth factors, vascular endothelial growth factor (VEGF) and their receptors.
6. Stops neo-vascularization
7. Stops cell proliferation and survival in leiomyoma cells but not in normal myometrial cells.[19]
8. Enhances the expression of matrix metalloproteinase (MMPs) and reduces the expression of tissue inhibitor of metalloproteinase (TIMPs) and collagens in cultured fibroid cells.
9. Ulipristil acetate (UPA) may impair fibroid tissue integrity by decreasing the deposition of collagen in the extracellular spaces.[20]

Median fibroid volume after successive courses of UPA treatment ranged from –63% to –72% as compared to the baseline value.

The significant reduction in fibroid size lasts for at least 6 months after treatment.

UPA shows several advantages:

1. It is faster than leuprolide in reducing the fibroid-associated bleeding.
2. It improves hemoglobin and hematocrit levels in anemic patients.
3. It brings a significant reduction in the size of fibroids, which lasts for at least 6 months after the end of the treatment.
4. UPA is a better tolerated when compared to leuprolide.
5. It keeps estradiol levels at mid-follicular phase range.
6. Reducing the frequency of hot flushes and has no impact on bone turnover.[7]

Recommendation: 5–10 mg per day for 3 months as per individual needs.[21]

Pharmacokinetics

Good bioavailability and rapid absorption.

Metabolism—extensively in liver by cytochrome (CYP) 3A4 protein-binding—more than 94% to plasma proteins including albumin, alpha1 acid glycoprotein and high-density lipoprotein.

Half-life elimination—32–38 hours. Its monodemethylated metabolite—27 hours.

Time to peak in serum—1 hour.[22]

Side Effects

- Headache and hot flushes, vertigo, functional ovarian cyst, nausea, acne, muscle pain sweating and tiredness
- Rarely changes in liver function seen
- Bone mineral density (BMD) not adversely affected
- Hyperplasia was observed.
- Dosage: 5 to 10 mg, daily, orally, 12 weekly.
- For 4 times in a year
- Within 1 week—70% is bleeding controlled.
- 80% had 25% reduction in volume of fibroid and improvement in pain.

Uses of Various Drugs

Controls bleeding, and reduction in the size of fibroids and increase the quality-of-life.

Some small studies demonstrated potential endometrial effect inhibiting implantation.[23]

UPA has been shown

1. To improve quality-of-life,
2. To reduce fibroid volume,
3. To induce amenorrhea in most of the women treated.

It is now approved for clinical use in both Europe and Canada.[24]

Ulipristal has successfully completed two-phase III clinical trials (PEARL I and II) proving its safety and efficacy for the treatment of symptomatic fibroids.

Uterine bleeding was controlled in 90% of patients receiving 5 mg dose and 98% with 10 mg dose while leuprolide acetate was 89%.

GnRH ANTAGONISTS

GnRH antagonists are a class of drugs, which antagonize the gonadotropin-releasing hormone receptor and act immediately to suppress the secretion of FSH and LH by blocking pituitary GnRH receptors, so no flare effect seen which inhibit the ovaries from producing estrogen.

The subsequent decrease in estradiol levels:

1. Leads to improvement in bleeding patterns and
2. A shrinkage in uterine fibroid size as early as 2 weeks after initiation of treatment.[25]

And within a shorter time in comparison to GnRH-a local tolerance is good because of its rapid onset of action, and avoidance of gonadotropin flare effect, patients experience faster symptom relief.

Further research is needed for dosing and its side effects.

Relugolix and elagolix is a FDA-approved oral tablet and can be given for 2 years to treat in perimenopausal women with heavy menstrual flow, compared to GnRH agonist given intramuscularly and only for short duration of 6–12 months with add back therapy.

CONCLUSION

- Fibroids are the most common non-malignant tumors of the reproductive age.
- As women continue to delay reproductive age.
- An increasing number of patients will require conservative or fertility-preserving treatment methods.
- Medical management of uterine fibroids may provide symptomatic relief of the uterine fibroid-related symptoms like heavy menstrual bleeding, pain along with the opportunity to preserve fertility.
- Also long-term medical treatment of fibroids seems possible today, especially in peri and premenopausal women.
- The most promising drugs belong to two categories:
  - Progesterone receptor modulators and orally active GnRH antagonist and GnRH agonist in depot formulations with add-back therapy.
  - Use of SPRM has emerged as a most viable option capable of offering women effective long-term medical management and prevent surgery altogether.
  - Future research is needed to evaluate the safety and efficacy of new depot formulation of GnRH antagonist in decreasing the size and symptoms of fibroids.

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Chapter

35

Drugs in Male Infertility

• Jiteeka Thakkar • Charumati V Pekhale • Rohan Palshetkar

Introduction

Around 50% of cases of infertility are due to male factors.[1,2] Either testis are malfunctioning or obliteration of duct.

There are several causes of male factor infertility, however, in most cases, the exact cause remains unknown.[1] Seminal fluid is rich in antioxidants that nourish and protect the sperm. They exist in two forms—an enzymatic and a non-enzymatic antioxidant system.[7] The enzymatic system includes glutathione peroxidase, superoxide dismutase, and catalase. These are naturally occurring enzymes in the sperm cell or seminal plasma and originates from the prostate. The non-enzymatic system, are consumed through diet or as supplements. Oxidative stress (OS) is an important contributor of infertility.[3]

Reactive oxygen species (ROS) are produced by the sperm cell in small quantities. There main functions are initiation of sperm capacitation, regulation of sperm maturation, and enhancement of cellular-signalling pathways.[4]

And thus high levels of ROS have paradoxical effects on sperm function, which results in infertility and deoxyribose nucleic acid (DNA) damage and lipid peroxidation.[5] Causes of increased ROS production are immature spermatozoa, leucocytes, varicocele and exogenous factors like testicular hyperthermia, environmental and habitual exposure.

Antioxidants help in counterbalancing ROS by maintaining the equilibrium in the redox potential desired for optimal sperm function.[6–7]

ANTIOXIDANTS IN MALE INFERTILITY

Mechanism of action of commonly used antioxidants.

Antioxidant compound	*Mechanism of action*
Ascorbic acid (vitamin C)	
Tocopherol (vitamin E)	Neutralises free radicals
Folate (vitamin B_9)	Scavenges free radicals
Selenium	Enhancement of enzymatic antioxidant activity
Zinc	Inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase
Carnitines	Neutralises free radicals and acts as an energy source
CoQ10	In its reduced form, scavenges free radicals intermediate in mitochondrial electron transport system
NAC	Enhances enzymatic antioxidant activity
Lycopene	Quenches free radicals

NAC: N-acetyl cystein

CLINICAL SCENARIOS AND ANTIOXIDANTS PRESCRIBED

Clinical circumstance	*Antioxidant*
Basic semen parameters	
Oligozoospermia	**Vitamin E, vitamin C, NAC, carnitines, CoQ10, lycopene, selenium and zinc**
	Vitamin E (300 mg)
	Vitamin E (180 mg), vitamin A (30 mg) and essential fatty acids or NAC (600 mg)
	NAC (600 mg) + other vitamins/minerals
	LC (2 g)
	CoQ10 (300 mg)
	NAC (600 mg) and selenium (200 µg)
	Folic acid (5 mg) + zinc (66 mg)
	Lycopene (2 mg)
Asthenozoospermia	**Vitamin E, vitamin C, NAC, carnitines, CoQ10, lycopene, selenium and zinc**
	Vitamin E (400 mg) + selenium (200 µg)
	Zinc (400 mg), vitamin E (20 mg) and vitamin C (10 mg)
	LC (2 g) and LAC (1 g)
	CoQ10 (300 mg)
	NAC (600 mg)
	NAC (600 mg) and selenium (200 µg)
	Lycopene (2 mg)
Teratozoospermia	**Vitamin E, NAC, lycopene, selenium and zinc**
	Vitamin E (400 mg) + selenium (200 µg)
	NAC (600 mg) and selenium (200 µg)
	Zinc (400 mg), vitamin E (20 mg) and vitamin C (10 mg)
	Lycopene (8 mg)
Advanced sperm function	
High SDF	**Vitamin E, vitamin C, zinc, selenium and folic acid**
	Vitamin E (1 g) + vitamin C (1 g)
	Vitamin C (400 mg), vitamin E (400 mg), β-carotene (18 mg), zinc (500 µmol) and selenium (1 µmol)
	LC (1500 mg); vitamin C (60 mg); CoQ10 (20 mg); vitamin E (10 mg); zinc (10 mg); folic acid (200 µg), selenium (50 µg); vitamin B_{12} (1 µg)
OS	**Vitamin E, vitamin C, NAC, selenium and zinc**
	Vitamin E (300 mg)
	Vitamin E (180 mg) and β-carotene (30 mg)
	Vitamin E (20 mg), vitamin C (10 mg) and zinc (400 mg)
	Vitamin E (400 mg) and selenium (225 g)
	NAC (600 mg)
Improving success rate of ART	**Vitamin E, vitamin C, lycopene, CoQ10, folic acid, selenium, zinc**
	Vitamin E (200 mg daily)
	Lycopene (6 mg), vitamin E (400 IU), vitamin C (100 mg), zinc (25 mg), selenium (26 g), folate (0.5 mg) and garlic (1 g)
	Vitamin E (600 mg)
	Vitamin C (1 g) + vitamin E (1 g)
Live-birth rate	**Vitamin E, vitamin C, carnitines, CoQ10, and zinc**
	CoQ10 (300 mg)
	Vitamin E (300 mg)
	Zinc (5000 mg)
	Vitamin E (1 g) + vitamin C (1 g)
	Carnitines: LC (2 g) + LAC (1 g/day)

Vitamin E (α-tocopherol) is an organic fat soluble compound. It reduces lipid peroxidation initiated by ROS by quenching free hydroxyl radicals and superoxide anions.

The percentage of motile spermatozoa in semen is directly related to levels of vitamin E in seminal plasma.[8] Lower levels of vitamin E were observed in the semen of infertile men.[9]

Vitamin C (ascorbic acid): It is present at concentration 10 times higher in seminal plasma than in blood serum.[10]

It neutralises hydroxyl, superoxide and hydrogen peroxide radicals providing protection against endogenous oxidative damage.[11] Seminal fluid analyses from infertile men with asthenozoospermia were found to contain lower vitamin C levels and higher ROS levels.[12]

Carnitines [L-carnitine (LC) and L-acetyl carnitine (LAC)] are also water-soluble antioxidants. It helps in sperm metabolism and helps increasing parameters like sperm motility.

There are studies where sperm cultured in media with carnitines and LAC showed better viability and motility.[13,14] They have antioxidant property and act on superoxide anions and hydrogen peroxide radicals thereby inhibiting lipid peroxidation.[15] Infertile men with oligoasthenoteratozoospermia showed significantly lower carnitine levels in semen sample.[16]

CoQ10 is a vital antioxidant omnipresent in almost all body tissues. It is particularly present at high concentrations in sperm mitochondria involved in cellular respiration and plays an integral role in energy production.[17] This contribution rationalises its use as a pro-motility and antioxidant molecule. Furthermore, co-enzyme Q10 (CoQ10) inhibits superoxide formation delivering protection against OS-induced sperm dysfunction. A significant negative correlation between CoQ10 levels and hydrogen peroxide and a linear correlation between CoQ10 levels in seminal plasma sperm count and motility was detected.[18]

N-acetyl cysteine (NAC): An amino acid that is converted in body tissues to cysteine, a precursor of glutathione. The latter is an important naturally occurring antioxidant capable of neutralising various ROS preventing their detrimental effects and reduces OS through scavenging hypochlorous acid and hydroxyl radicals.[19–21]

Selenium: An essential trace element and protects sperm DNA against OS damage in a mechanism that is not very well-understood and augments the function of glutathione. More than 25 selenoproteins exist, such as phospholipid hydroperoxide glutathione peroxidase (PHGPX)[22] and sperm capsular selenoprotein glutathione peroxidase,[23] which help maintain sperm structural integrity.[24] Selenium deficiency has been most commonly associated with morphological sperm mid-piece abnormalities and impairment of sperm motility.[25]

Zinc: Another essential trace element.[26] It plays a vital role in the metabolism of RNA and DNA, signal transduction, gene expression, and regulation of apoptosis. Its antioxidant properties are thought to result from its ability to decrease production of hydrogen peroxide and hydroxyl radicals through antagonising redox-active transition metals, such as iron and copper.[27] Zinc concentrations of seminal plasma were found to be significantly higher in fertile men in comparison with subfertile men.[28] Zinc is thought to deliver an important protective effect on sperm structure. Sperm flagellar abnormalities, such as hypertrophy and hyperplasia of the fibrous sheath, axonemal disruption, defects of the inner microtubular dynein arms, and abnormal or absent mid-piece have all be associated with zinc deficiency.

Folic acid: Folic acid (vitamin B_9) is involved in nucleic acid synthesis and amino acid metabolism.

Free radical scavenger: Folic acid intake was associated with an elevation in the reduced oxidized glutathione ratio.[29]

Lycopene: Lycopene is a carotenoid found in fruits and vegetables. It is known for its powerful ROS quenching abilities.[30] Lycopene is found at high concentrations in human testes and seminal plasma. Infertile men tend to have lower levels of lycopene compared to fertile men.[31]

However, it is important to note that the benefits of supplements, including antioxidants and vitamins, in treating male infertility are of questionable clinical utility. Existing data are inadequate to provide specific recommendations for the use of these agents in treating male infertility. Patients need to be counselled regarding the same.

CONDITIONS AND PROPOSED TREATMENT

Hypogonadotropic hypogonadism (HH), the underlying cause of the disorder should be determined before initiating treatment. The congenital form idiopathic hypogonadotropic hypogonadism (IHH), also known as isolated gonadotropin-releasing hormone (GnRH) deficiency, is a rare genetic disorder associated with defects in the production and/or action of GnRH.

The usual first-line drug for the treatment of IHH is human chorionic gonadotropin (hCG), which is used to restore testosterone levels and spermatogenesis. The response to hCG treatment correlates with the size of the testis before initiation of treatment.[32–34] Initial treatment involves hCG injections (1,500-2,500 IU, twice weekly) followed by follicle stimulating hormone (FSH) if indicated, after testosterone levels are normalized with hCG. If medical treatment fails to result in a pregnancy but some sperm are found in the ejaculate, referral for assisted reproductive technology (ART) is recommended.

Selective estrogen receptor modulators (SERMs) have been used off-label as an alternative treatment to increase testosterone and sperm density in men with adult-onset IHH. However, the evidence for this treatment is limited, with only a small number of studies reporting successful pregnancies in men with adult-onset HH.[35,36]

Secondary causes of HH include, pituitary infiltrative disorders (*e.g.* hemochromatosis, tuberculosis, sarcoidosis, histiocytosis), pituitary or suprasellar tumors, exogenous androgen use, other medications (*e.g.* chronic narcotic exposure), prior head trauma, pituitary apoplexy, hyperprolactinemia and severe chronic illness.[37] The primary treatment for secondary HH is directed towards addressing the underlying disorder.

Aromatase inhibitors (AIs), human chorionic gonadotropin (hCG), and selective estrogen receptor modulators (SERMs) are medications that work through different mechanisms to increase endogenous testosterone production. Each of these agents can be used individually or in combination to raise serum testosterone levels without negatively affecting spermatogenesis. It is important to note that while hCG is approved by the Food and Drug Administration (FDA) for use in men with hypogonadotropic hypogonadism (HH), the other medications are not approved for this purpose. Additionally, it should be recognized that the goal of optimizing testosterone levels in infertile males may focus on alleviating symptoms, but the symptomatic outcomes and benefits may not be comparable to those achieved with standard exogenous testosterone replacement therapy.

The conversion of testosterone to estrogen occurs peripherally through the enzyme aromatase. AIs are oral medications that inhibit this conversion, resulting in a relative decrease in serum estradiol levels, an increase in luteinizing hormone (LH) secretion by the pituitary gland, and a relative increase in serum testosterone concentration. Clinicians may consider the use of AIs for men with testosterone deficiency and elevated estradiol levels.[38,39] hCG which is given by parenteral route acts as an LH analogue, stimulating testosterone production by the Leydig cells. SERMs are oral medications with centrally antiestrogenic effects that impede

the negative feedback of the hypothalamic-pituitary–testis axis.

Clomiphene Citrate

It leads to increase in LH and FSH production by the pituitary gland. The increased LH production, in turn, stimulates Leydig cell production of testosterone. Clinically, either hCG or SERMs can be considered for optimization of testosterone in men with low or normal serum LH levels. However, men who show elevated LH with primary hypogonadism, may have limited testosterone response due to inherent testicular dysfunction.

Exogenous FSH can be used in the treatment of HH to initiate and maintain spermatogenesis. In some studies, exogenous FSH has been used in males without HH (baseline FSH in or slightly above the normal values) to improve the fertility chances. The dosage of FSH used was 150 IU per day for a period of 12 weeks. A meta-analysis including 15 trials comparing the effects of FSH with placebo or no treatment showed improvement in semen parameters and pregnancy rates with the use of FSH. This study included cases with assisted and unassisted with ART.[40]

Non-obstructive Azoospermia (NOA)

For patients with NOA, spermatogenesis should be ideally optimised to improve the chances of sperm recovery with surgical sperm retrieval. Use of SERMs, AIs and hCG to manipulate reproductive hormones to improve sperm parameters in ejaculate or improvement of surgically retrieved sperms has been off label. One study assessed men with NOA, who received clomiphene citrate prior to microsurgical testicular sperm extraction (micro-TESE). 11% of patients had sperm recovery in the ejaculate without needing micro-TESE. Surgical sperm retreval (SSR) in the remaining patients had sperm retreieved in 57.7% cases *versus* 33.6% in the control group.[41]

A trial compared letrozole, an aromatase inhibitor (AI) to placebo in cases of NOA. Not all NOA cases with letrozole showed sperms in ejaculate. There were no sperm recovery in the ejaculate of the placebo group. None of the groups had unassisted pregnancies.[42] A study compared the effects of hCG before surgical approach to no treatment in cases of NOA. There was no statistically significant difference in SSR, pregnancy rate or live birth rate between the two groups.[43]

Another small study compared FSH to no treatment prior to TESE. Surgical SSR in the FSH group was 64% as compared to 33% in the no treatment group.[44]

Men suffering with cancers should be encouraged to freeze semen, preferably multiple samples before they begin with chemotherapy or other treatment that may affect fertility in men.

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Chapter 36

Drugs in Pelvic Inflammatory Disease

• Priti Vyas • Suchitra N Pandit

Introduction

An acute infection of the female upper genital tract tissues, including the uterus, fallopian tubes, and/or ovaries, along with or without the surrounding pelvic organs, is known as pelvic inflammatory disease (PID).[1] It might be mild-to-moderate PID, defined as the absence of a tubo-ovarian abscess, or severe illness, characterized as the presence of a tubo-ovarian abscess or severe systemic symptoms. Cervicitis, salpingitis, endometritis parametritis, and pelvic peritonitis are just a few of the possible long-term effects on fertility that this condition can have. It can also lead to persistent pelvic pain, adhesions, and ectopic pregnancies. When compared to women without a history of PID, a woman's chance of an ectopic pregnancy rises seven times after only one incident. After a single episode of PID, about 12% of women are infertile; after two episodes, nearly 25%; and after three episodes or more, over 50%.

INCIDENCE

2–8%. It is one of the most frequent but harmful infection that affects women who are of reproductive age. 15 to 20% of women with PID are thought to experience the problems, which may potentially necessitate surgical treatment. The effects of PID can seriously harm reproductive health in addition to causing emotional stress.

The term 'silent PID' refers to a condition when there are little or no symptoms, yet tubal reasons of infertility and/or serologic proof of prior sexually transmitted diseases (STDs) are present without any prior history of overt illness.[2] These are particularly the ones that require prevention if PID complications and their consequences are to be avoided.

India PID incidence: According to National Family Health Survey (NFHS)[2] data, it is estimated that the prevalence of symptoms suggestive of sexually transmitted infection (STI)/reproductive tract infection (RTI) in women was in the range of 23–43%, while in men it is in the range of 4–9% **(Table 36.1)**.[3,4]

ETIOLOGY

Microorganisms

- *Chlamydia trachomatis* and *Neisseria gonorrhea*
- Anaerobic gram-negative rods, *Mycoplasma genitalium* and bacterial vaginosis
- Often polymicrobial infection with *Gardnerella vaginalis*, *Hemophilus influenza*, anaerobes, enteric gram-negative rods. Majority are sexually transmitted and remaining are caused by *E coli*, Group-B streptococci, *Bacteroides fragilis* and lower genital tract organisms.

- Genital tuberculosis is also implicated as a common cause of pelvic inflammation in India.[5–9]

More details will be with the clinical features.

Risk Factors

- Previous history of PID
- Untreated chlamydia or gonococcal infection, with increased risk with each subsequent reinfection
- Risk factors associated with STI, such as
  - Multiple sexual partners,
  - Non-usage of barrier contraception,
  - Smoking, recreational drugs,
  - Oral contraceptive (OC) pills
  - Young adolescents with risky sexual behavior
  - Older women due to menopausal changes in vaginal mucosa, etc.

Abortions, puerperal sepsis, and intrauterine device (IUD) insertions are the most frequent causes in Indian settings.

Table 36.1: Organism/infection—symptoms[3]

STI/RTI	*Pathogen*	*Clinical features*
Gonorrhoea 'drip'	*Neisseria gonorrhoea*	• Vaginal muco-purulent discharge • Dysuria and urethritis
Trichomoniasis	*Trichomonas vaginalis*	• Asymptomatic • Foul-smelling, foamy, and greenish vaginal discharge • Foul-smell with itching and burning • pH >5
Chlamydia	*Chlamydia trachomatis*	• Produces minimal symptoms, even when there is an upper genital tract infection (silent PID). • An often 'beefy' crimson, friable, and purulent cervical discharge that bleeds readily.
Bacterial vaginosis	Overgrowth of anaerobes like *Gardnerella vaginalis*	• Not necessarily sexually transmitted. • Vaginal discharge that smells fishy, greyish in colour. • May not have itching or burning. • pH >4.5
Candidiasis	*Candida albicans*	• A white, curd-like vaginal discharge • Moderate-to-severe vulval or vaginal itching and burning • No foul smell • pH <4.5
Presenting with pain in lower abdomen		
Pelvic inflammatory disease (PID)	• *Neisseria gonorrhea* • *Chlamydia trachomatis* • Anaerobes	• A lowered stomachache • Vaginal discharge • Heavy, irregular vaginal bleeding is a sign of menstrual abnormalities. • Dysmenorrhea, pain during sexual activity, or dyspareunia • Dysuria tenesmus • Lower back pain • Discharge from the cervix or vagina • Congestion or ulcers • Stiffness in the lower abdomen • Cervical movement discomfort • Pelvic mass presence • Uterine/adnexal soreness

PATHOGENESIS OF PID[10]

- Ascending
- Hematogenous
- Local spread

PID occurs basically in 2 stages for most of the cases:

- Acquiring a sexually transmitted, frequently asymptomatic vaginal or cervical infection. These germs directly ascend to the upper vaginal canal, infecting and causing inflamation of these organs.
- Salpingitis with spread to parametrium or bowel. The infection may spread through hematogenous or direct purulent discharge from the tubes into the pelvic cavity causing cute peritonitis or even perihepatitis—Fitz-Hugh Curtis syndrome
- Cervical mucus forms a protective barrier, during ovulation and menstruation the hormonal changes decrease the efficacy of this barrier and vaginal inflammation would do the same.
- When indigenous flora in the lower genital tract is out of balance due to antibiotic therapy, typically nonpathogenic organisms might overgrow and ascend.

CLINICAL FEATURES

PID is often an acute condition with varied presentation depending on the nature of the causative organism but occasionally can be a chronic presentation over weeks. It is often a diagnosis of exclusion with no single diagnostic criteria. The differential diagnosis of ectopic, appendicitis, torsion have to be ruled out before coming to a definitive diagnosis.

It can be difficult to diagnose PID, if it is mild or asymptomatic since neither the patient nor the doctor will notice the clinical signs. Even individuals with mild or asymptomatic PID may be at risk for infertility when nonspecific symptoms or indicators (such as abnormal bleeding, dyspareunia, and vaginal discharge) are disregarded. Given the complexity of diagnosis and the potential for serious harm to women's reproductive health, it is best to have a low threshold for suspicion and the clinical diagnosis of PID.

The signs and symptoms may be one or more of the following:

- Lower abdominal pain with
- Dyspareunia
- Vaginal and/or cervical discharge-yellowish or purulent, positive whiff test, foul smell, or fishy odor; cervical friability
- Nausea, vomiting and bloating with or without loose motions
- Menorrhagia with irregular menstrual bleeding
- Dysmenorrhea
- Dysuria
- Fever with chills
- In case of severe infections: Severe pain with high fever, tachycardia, nausea, vomiting and right upper quadrant pain
- Lower abdominal pain and tenderness with or without guarding
- Uterine, adnexal and cervical movement tenderness
- Friable cervix, strawberry vaginitis.

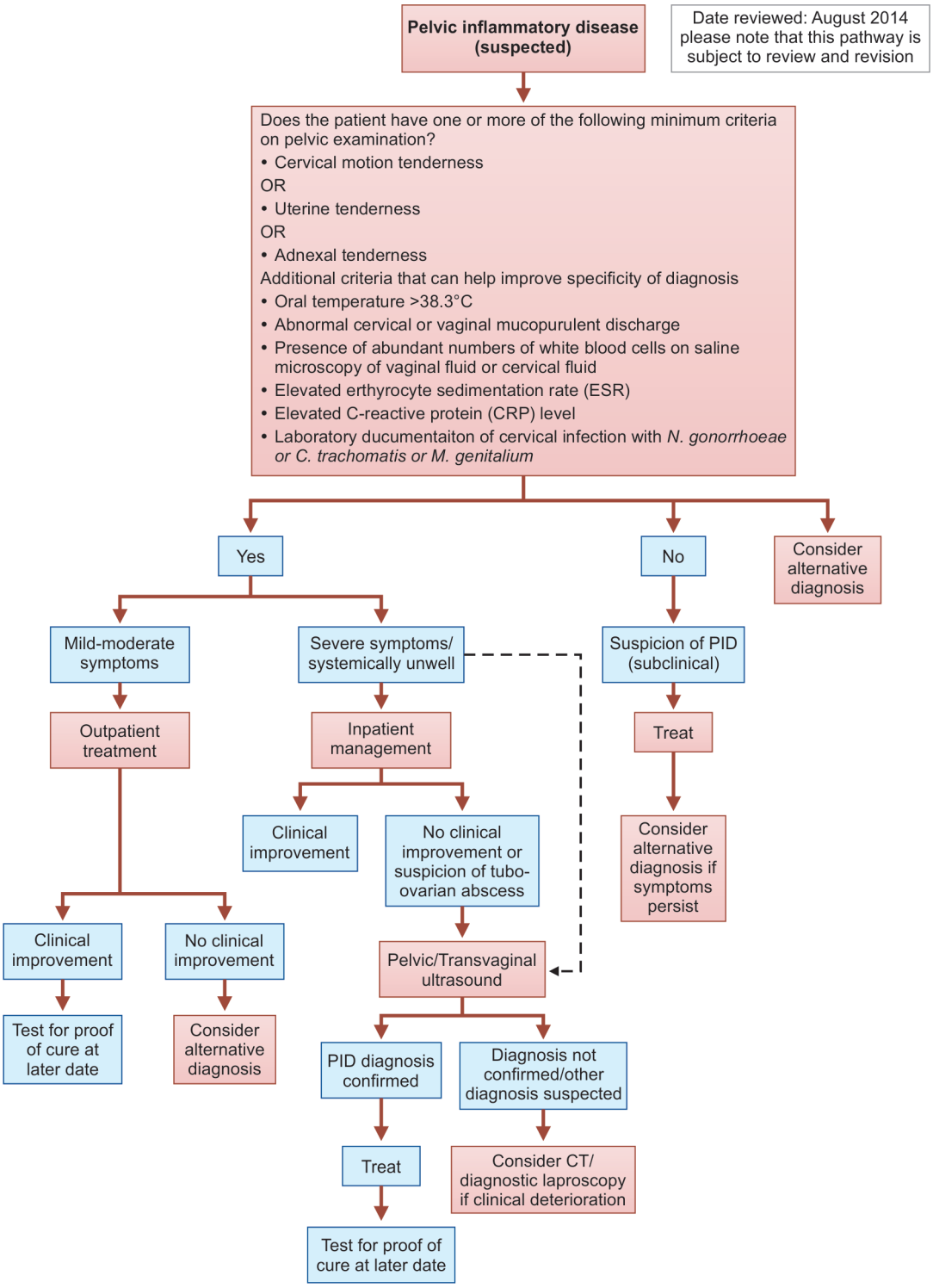
DIAGNOSIS (Flowchart 36.1)

The specificity of the diagnosis is increased when the lower genital tract inflammatory symptoms listed below are present in addition to one of the three minimal requirements.

In addition to the minimum clinical criteria listed below, one or more of the following additional criteria may be used to support the diagnosis of PID:[10–12]

- Oral temperature >38.3°C (>101°F)
- Abnormal cervical mucopurulent discharge or cervical friability
- Saline microscopy of vaginal secretions showing plenty of white blood cells
- Heightened erythrocyte sedimentation rate
- Increased C-reactive protein

Flowchart 36.1: Clinical diagnosis of PID



CT: Computed tomography

- Nucleic acid amplification test (NAAT) evidence of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

Other tests specifically can be:

- Polymerase chain reaction (PCR)
- Chlamydia antibodies: Immunoglobulin G (IgG) and immunoglobulin M (IgM)
- Test for other infections: Syphilis, human immunodeficiency virus (HIV) and urinary tract infection (UTI)
- Endometrial biopsy is not routinely done but if done will show histopathologic evidence of endometritis—acute or chronic
- Imaging—ultrasonography (USG) and magnetic resonance imaging (MRI)—will show thickened tubes or tuboovarian (TO) mass or hydrosalpinx or pelvic vascularity and congestion on doppler,
- Laparoscopic diagnosis.

There are two main approaches to STI/RTI diagnosis and management **(Tables 36.2 and 36.3)**:

- The etiological approach
- The syndromic approach

However, syndromic approach has its limitations of missing out on asymptomatic infections completely **(Tables 36.4)**.

Clinical diagnosis of PID

See **Flowchart 36.1.**[13]

Complications of STI

- PID, ectopic pregnancy, infertility and chronic pelvic pain
- Increased chance of contacting other infections
- Preterm labour, stillbirths, and miscarriages
- Neurological, cardiovascular, and other systemic complications
- Chronic pain.

PREVENTION

The best prevention is[14–16]

- Primary prevention of infection in both sexes
- Secondary prevention—early treatment and stoppage of spread

Both at local and national level effective STI control programs have to be implemented.

These should include:

- Medical management
- Education of individuals for adopting healthy behaviours
- Screening for STI, especially the at risk individuals
- Prevention and treatment for both partners.

TREATMENT

Aims

Diagnose and early treatment is important for:

- Eradication of infection
- Relief of symptoms
- Preventing spread to partner
- Preventing long-term sequel

The type of treatment methods are commonly referred to as the 'six Cs'[3]

- Counselling, educating the patient
- Contact tracing
- Condom usage
- Compliance check
- Come back for a follow-up
- Cure the patient.

There are three ways to treat patients with PID

- Presumptive treatment
- Etiological treatment
- Syndromic management

Presumptive treatment: When there is no other known cause of the pelvic or lower abdominal pain other than PID, or if one or more of the following three minimum clinical criteria are present on pelvic examination: Cervical motion tenderness, uterine tenderness, or adnexal tenderness, presumptive treatment for PID—was frequently used, began. There is no perfect course of treatment, and it is unknown whether subclinical PID patients who receive early treatment will fare better in the long run.

Table 36.2: Clinical features of common STI[3]	
Clinical feature	*Pathogens*
Unusual vaginal discharge	BV, chlamydia, gonorrhoea, trichomonas infection, vaginal yeast infection
Genital itching	BV, trichomonas infection, vaginal yeast infection
Abnormal and/or heavy vaginal bleeding	Chlamydia, gonorrhoea and mixed anaerobic infection. Gonorrhoea (*Note:* This symptom is often caused by factors other than STI)
Post-coital bleeding	Chlamydia, gonorrhoea, chancroid, genital herpes
Lower abdominal pain (pain below the belly button; pelvic pain)	Chlamydia, gonorrhea and chlamydia, gonorrhea and mixed anaerobic infection.
Repetitive vaginal candidiasis	HIV/AIDS
Painful intercourse	
On the mouth, lips, genitals, anus, or adjacent regions, blisters or ulcers (sores)	Chancroid, genital herpes, and syphilis
Dysuria	Chlamydia, genital herpes, trichomonas infection, and gonorrhoea
Itching or tingling sensation	Genital herpes, candidiasis Genital herpes, candidiasis
Jaundice, fever, headache, muscle pain, yellower urine	Hepatitis B, hepatitis C
Genital warts on the anus or nearby places	HPV (genital warts)
Mild liver inflammation, fever, exhaustion, headaches, and other flu-like symptoms	CMV
Skin lesions which are small, dimpled lumps that are often painless and itchy and are flesh-colored, however they can also be white, yellow, or pink	*Molluscum contagiosum*
Chronic ulcers on the genitals or anus, small, red lesions or ulcers in the anal or genital region, lymph node enlargement in the anal or genital region	LGV
Anus, genitalia, or mouth-red nodules or eruptions under the skin that bleed readily, ulcerate, and become sensitive.	Donovanosis

Table 36.3: Comparison between etiologic and syndromic approach	
Etiological approach	*Syndromic approach*
Can get exact diagnoses with lab test	May go wrong, *e.g.* gonorrhoea and chlamydia with vaginal discharge
Over treatment avoided	Over treatment may happen
Patient has to come back for results, hence treatment delayed	First visit treatment started
Chances of lost to follow-up	No loss to follow-up
Cost of lab test	Relatively less expensive

Table 36.4: Treatment protocols

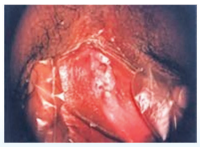
OPD treatment		
Mild-to-moderate infections	*Drug*	*Duration*
I.	Third generation cephalosporin ceftizoxime or cefotaxime 1–2 g doxycycline, 100 mg, BD with metronidazole, 500 mg, twice daily	Doxy and metronidazole to complete a 2-week course Third generation cephalosporin is less effective on anaerobes, hence use metronidazole
II. Alternative regimen	Ceftraixone, 250 mg, IM, single dose Plus azithromycin, 1 g, one dose every week for 2 weeks	
III.	Ceftraixone, 250 mg, IM, single dose or cefoxitin 2 g, IM, once Plus doxycycline, 100 mg, BD, with or without metronidazole 500 mg, BD	Doxy and metronidazole to complete the 2-week course
In patient therapy or allergy to beta-lactams or severe infections including tubo-ovarian abscess or endometritis	Tubo-ovarian abscess requires surgical management, if no response to medical management	
I.	Clindamycin 900 mg iv 8 hourly with Gentamycin 2 mg/kg loading dose followed by 1.5 mg /kg 8 hrly	After clinical improvement—Clindamycin (450 mg, orally, QID) or doxycycline (100 mg, orally, BD) to complete the 2-week course
II.	Azithromycin, 2 g stat oral Plus levofloxacin, 500 mg, OD	14 days
III.	Levofloxacin, 500 mg, OD or ofloxacin, 400 mg, BD, or plus metronidazole, 500 mg, BD Moxifloxacin, 400 mg, BD	14 days
IV.	Inj. cefotetan, 2 g, BD, or cefoxitin 2 g, IV, 6 hrly, plus doxy, IV, 100 mg, BD	After clinical improvement—doxy, 100 mg, BD, for 14 days
V.	Ampicillin/Sulbactam, 3 g, IV, 6 hrly plus doxycycline, 100 mg, IV, BD	After clinical improvement—doxy, 100 mg, BD, for 14 days

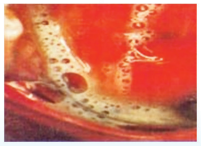
Etiological treatment: It is based on laboratory diagnosis, smears, and blood work to document the infection and then specific treatment is given depending on the diagnosis or pathologic agent identified. This being ideal situation; however, may not always be available due to paucity of lab supplies or skilled manpower or specialised equipment needed to diagnose accurately. Precious time is lost while the results are awaited for the treatment to start. Sometimes the patient may be lost to follow up while awaiting results.

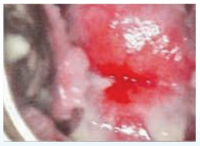
Syndromic management: The World Health Organization (WHO) created the syndromic management strategy for STI/RTI management in 1991 to overcome the

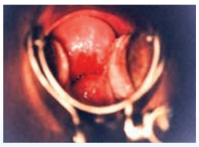
Flowchart 36.2: Management of vaginal discharge in females[3]

Syndrome: Vaginal discharge


Vaginitis


Trichomoniasis


Cervical herpes


Cervical herpes

Causative organisms of vaginitis
- *Trichomonas vaginalis (TV)*
- *Candida albicans*
- *Gardnerella vaginalis, Mycoplasma*

Causative organisms cervicitis
- *Neisseria gonorrhoea*
- *Chlamydia trachomatis*
- *Trichomonas vaginalis*
- Herpes simplex virus

History
- Rule out pregnancy
- Discharge type—smell, colour consistency amount
- Itching in genital area
- Urinary frequency burning
- Ulcer/swelling on inguinal region
- Sexual partner genital complaints
- Lower abdomen or back pain

→

Examination

Per speculum—vaginitis/cervicitis

- **Vaginitis**
  - Trichomoniasis—greenish frothy discharge
  - Candidiasis—curdy white
  - Bacterial vaginosis—adherent discharge
  - Mixed infections may present with atypical discharge

- **Cervicitis**

Cervical erosion/cervical ulcer/muco-purulent cervical discharge
- Bimanual pelvic examination to rule out PID
- If not possible, treat both for vaginitis and cervicitis

↓

Laboratory investigations (if available)

- Wet mount microscopy of the discharge for *Trichomonas vaginalis* and clue cells
- 10% KOH preparation for *Candida albicans*
- Gram stain of vaginal smear for clue cells seen in bacterial vaginosis
- Gram stain of endocervical smear to detect gonococci

↓

Treatment

Vaginitis (TV+BV+Candida)
- Tab. secnidazole, 2 g, orally, single dose or tab. tinidazole, 500 mg, orally, BD for 5 days
- Tab. metoclopramide, 1/2 hr, before tab. secnidazole, (prevention of GI SE)
- For candidiasis—tab. fluconazole, 150 mg, orally, single dose or local clotrimazole, 500 mg, vaginal pessaries once

Treatment for cervical infection (chlamydia and gonorrhoea)

Tab. cefixime, 400 mg, orally, single dose
plus azithromycin, 1 g, 1 hour before lunch. If vomiting within 1 hour, give antiemetic and repeat
- If vaginitis and cervicitis are present treat for both
- Instruct client to avoid douching

Pregnancy, diabetes, HIV may also be influencing factors and should be considered in recurrent infections
- Follow-up after one week

Specific guidelines for partner management

Cervicitis: Treat all partners for gonorrhoea and chlamydia.

Vaginitis: Generally, partner treatment is not required. If partner is symptomatic, treat partner for the symptom.

Advise sexual abstinence during the course of treatment
Give condoms, and also educate about correct consistent use
Call for FU visit after 7 days

Management in pregnant women

PS-rule out pregnancy complications, like abortion, premature rupture of membranes

Treatment for vaginitis (TV+BV+Candida)

In first trimester of pregnancy
- Local treatment with clotrimazole vaginal pessary/cream only for candidiasis.
- Oral fluconazole is contraindicated in pregnancy.
- Metronidazole pessaries or cream intravaginally, if trichomoniasis or BV is suspected.

In second and third trimesters oral metronidazole can be given
- Tab. secnidazole, 2 g, orally, single dose or tab. tinidazole, 500 mg, orally, BD, for 5 days
- Tab. metoclopropramide, ½ hr before tab. metronidazole (prevent GI SE)

Management of pregnant women with cervicitis

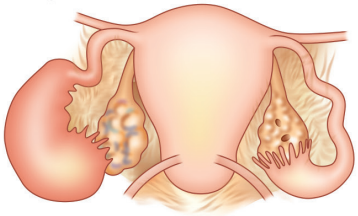
Examined by doing a PS and PV examination and treated for gonococcal as well as chlamydial infections.

Cephalosporins for gonococcal infection are safe and effective in pregnancy
- Tab. cefixime, 400 mg, orally, single dose or
- Ceftriaxone, 125 mg by intramuscular injection +
- Tab. erythromycin, 500 mg, orally four times a day for seven days or
- Cap. amoxicillin, 500 mg, orally, three times a day for 7 days to cover chlamydial infection

Quinolones (like ofloxacin, ciprofloxacin), doxycycline are contraindicated in pregnant women

Flowchart 36.3: Management of lower abdominal pain in females[3]

Syndrome: Lower abdominal pain



Pelvic inflammatory diseases

Causative organisms
- *Neisseria gonorrhoea*
- *Chlamydia trachomatis*
- *Mycoplasma, Gardnerella,* Anaerobic bacteria (*Bacteroides* sp., gram-positive cocci)

History
- Pain in lower abdo or pelvic pain
- Fever
- Vaginal discharge
- Menstrual irregularities, like heavy, irregular vaginal bleeding
- Dysmenorrhoea
- Dyspareunia
- Dysuria, tenesmus
- Low backache
- Contraceptive use like IUD

Examination
- **GE:** TPR-BP
- **PS examination:** Vaginal/cervical discharge, congestion or ulcers
- **PA examination:** Lower abdominal tenderness or guarding
- **Pelvic examination:** Uterine/adnexal tenderness, cervical movement tenderness

Note: A urine pregnancy test should be done in all women suspected of having PID to rule out pregnancy.

Laboratory investigations (if available)
- Wet smear examination
- Gram stain for gonorrhoea
- CBC and ESR
- Urine microscopy for pus cells

Differential diagnosis
- Ectopic pregnancy
- Twisted ovarian cyst
- Ovarian tumour
- Appendicitis
- Abdominal tuberculosis

Treatment (out-client treatment)

In mild-or-moderate PID (in the absence of tubo-ovarian abscess), out-client treatment can be given.

Neisseria gonorrhoea, *Chlamydia trachomatis*, and anaerobes all require therapy.
- Cefixime, 400 mg, tablet stat, metronidazole, 400 mg, twice daily for 14 days, together with doxycycline, 100 mg, twice daily for 2 weeks, are both prescribed to treat chlamydial infection. Tab. ibuprofen, 400 mg, TDS, for 3–5 days.
- 150 mg of ranitidine, BD, orally, to prevent acidity

- Remove any intrauterine devices under cover of 24–48 hours of antibiotic treatment.
- Emphasize abstinence while receiving therapy and instruct on how to use condoms properly and consistently.
- Watch for 3 days.
- Refer for in-client therapy, if there is no improvement (*i.e.* no fever, decreased stomach soreness, decreased cervical movement, increased adnexal and uterine tenderness), or if the symptoms worsen.

When the diagnosis of a client with acute PID is unclear or when surgical emergencies, such as ectopic pregnancy or appendicitis cannot be ruled out, hospitalization should be strongly considered.

Other reasons for inpatient treatment
- The client is unable to adhere to or endure an outpatient regimen.

- There is suspicion of a pelvic abscess;
- Severe sickness prevents care on an outpatient basis;
- The client has not responded to outpatient therapy.

Note: The district hospital should be referred to any clients who need to be hospitalized.

Syndrome specific guidelines for partner management
- Treat all partners
- Treat male partners for urethral discharge (gonorrhoea and chlamydia)
- Advise sexual abstinence during the course of treatment

- Provide condoms, educate on correct and consistent use
- Refer to ICTC for HIV and syphilis testing

Inform about the complications if left untreated and sequelae

Management of pregnant women

PID is uncommon during pregnancy, however,
- Pregnant women who are suspected of having PID should be sent to the district hospital for hospitalization and treatment with a parenteral regimen that is safe during pregnancy.

- It is not advised to use doxycycline when pregnant.

Note: The first 3 months of pregnancy are typically not the best time to take metronidazole. However, it should not be withheld in the event of a critically acute PID, which is an emergency.

limitations of etiological and presumptive diagnosis. The syndromic management flow charts are the gold standard of care in the majority of resource-constrained situations when the etiological diagnosis cannot be made accessible for the therapy to start and if laboratory testing is not available or is difficult to get. Clinical algorithms based on an STD syndrome, based on clinical signs and symptoms that the patient presents with, have been made. This approach may land up overtreating the partners, but the treatment is started in time and on the first visit itself.

Based on groups of symptoms and indicators that are simple to recognize, STI are categorized into syndromes, and the most prevalent organisms that cause each syndrome are treated. By employing or distributing pre-packaged, color-coded STI/RTI medication kits, standardized therapy is provided. This method has good cure rates, since it treats patients right away and involves little to no laboratory expense. The guidelines mentioned here are developed by National Aids Control Society, New Delhi, in association with World Health Organization, include management of symptomatic infections related to urethral discharge syndrome, vaginal discharge syndrome, anorectal infection; genital ulcer disease syndrome; and lower abdominal pain syndrome.[3]

Rationale for the Treatment Regimes

The diagnosis for the majority of PID patients is frequently clinical, and prompt initiation of a broad-spectrum empirical therapy is required. Because upper genital tract infection can still occur even if endocervical screening for *N. gonorrhoeae* and *C. trachomatis* is negative, the PID regimens should also be effective against these pathogens. Women with PID have anaerobic bacteria and BV that can destroy the tubal and epithelial lining of the vaginal canal. Anaerobic organisms in the upper vaginal tract are more successfully eliminated when metronidazole is added to intramuscular (IM) or oral PID treatments.[6]

The Antibiotics Given against the Common Pathogens[17–19]

- Cephalosporins: Gonococcal infection
- Azithromycin, doxycycline: *Chlamydia trachomatis*
- Metronidazole: Anaerobes, gram negative and positive

Inpatient therapy or hospitalization will be needed if:

- Noncompliance or
- Severe side effects to oral therapy or
- Fever of more than 38.5°C (101°F) or severe clinical illness with nausea and vomiting
- There is need for surgical drainage of infection or abscess.
- Pregnancy with PID
- Doubtful diagnosis
- Other diseases, such as appendicitis and ectopic pregnancy can not be ruled out.
- The patient is unable to tolerate or failed to respond to outpatient regimen.
- Within 3 days of beginning antibiotic medication, the patient cannot return for a clinical check-up.

Efficacy of Treatment Regimens

Some experts recommend to admit all patients with PID to start treatment with parenteral antibiotics. But efficacy for outpatient *vs* inpatient therapy is similar with similar results and long-term sequel as per the—pelvic inflammation disease evaluation clinical health (PEACH) trial.

General Advice, Follow-up and Partner Treatment

- Monitor the response to treatment in 48–72 hours—if no improvement—admit and start parental therapy. If response good, call for follow-up at one week, to review cure and reports, if any done. Ensure completion of treatment.
- Encourage abstinence from sex until treatment is finished and symptoms have subsided.

- All sexual partners or from the last 60 days should be investigated and treated.
- *Counsel:* The couple and the patient about safe sex practices, so as to prevent repeation of episodes, also about genital cancers and barrier contraception—condoms.
- Instruct to avoid douching.
- If PID diagnosed—test for gonorrhoea, chlamydia, HIV, and syphilis.
- Immunisation status—for hepatitis B, human papillomavirus (HPV).
- Regardless of whether the spouse has had treatment or not, repeated testing should be done 3 months following therapy, if chlamydial or gonococcal PID was diagnosed.

SPECIAL CASES

PID in HIV Positive Patients

Higher risk of tubo-ovarian abscess and severe disease. Treatment protocols are same but in patient therapy may be needed for the immune suppressed.

Pregnancy

PID: High risk of premature birth and maternal morbidity. In conjunction with an infectious disease expert, the pregnant PID patients need to be hospitalized and given intravenous (IV) antibiotics. Avoid using medications known to be harmful during pregnancy, such as tetracyclines and quinolones. For PID, a 14-day course of cefotaxime, azithromycin, and metronidazole may be prescribed. By doing a speculum examination, pregnancy problems, such as abortion and premature rupture of membranes should be ruled out in patients with STI, PID, and UTI.

Treatment for Vaginitis [Trichomonal Vaginitis (TV), Bacterial Vaginosis (BV) and Candida][11,14]

In First Trimester of Pregnancy

- Only use clotrimazole vaginal pessaries or cream for localized candidiasis therapy.
- Flucanozole should not be used orally when pregnant.
- When trichomoniasis or BV are detected, metronidazole pessaries or cream should be used intravaginally.

In Second and Third Trimesters of Pregnancy

Oral metronidazole can be given.

- Tab. secnidazole, 2 g, orally, single dose or metronidazole, 400, TDS, for 5 days or tab. tinidazole, 500 mg, orally, BD, for 5 days.
- Tab. metoclopropramide taken half hour before tab. metronidazole to prevent nausea/vomit.

Management of Pregnant Women with Cervicitis

Look for and treat gonococcal as well as chlamydial infections.

- Cephalosporins to cover gonococcal infection are safe and effective in pregnancy.
  - Tab. cefixime, 400 mg, orally, single dose or ceftriaxone, 125 mg, by intramuscular injection plus
  - Tab. erythromycin, 500 mg, orally, four times a day for 7 days or
- Cap. amoxicillin, 500 mg, orally, three times a day for 7 days to cover chlamydial infection.
- Quinolones (like ofloxacin, ciprofloxacin), doxycycline are contraindicated in pregnant women.

Postmenopausal Patients

Can have similar complaints but keep in mind the differential diagnosis of malignancy while diagnosing tubo-ovarian abscess in this population.

Intrauterine Devices

The risk for PID associated with IUD, was higher with the first and second generation IUD. With the third generation Cu-IUD and LNG-IUS use, the risk of PID is primarily confined to the first 3 weeks after insertion. If an IUD user receives a diagnosis of PID, the IUD

does not need to be removed; full treatment according to the local recommendations has to be given followed by a close follow-up. If no clinical improvement occurs within 48–72 hours of initiating treatment, then should consider removing the IUD.[7–9]

Tubo-ovarian Abscess

Seen in around 10% of women with PID, an inflammatory mass involving fallopian tube, ovary, and pelvic organ, with pus collection and adhesions. Can be a sequel to PID. It can be potentially life-threatening requiring medical and surgical management. Necrosis within the mass can result in further increasing infection and anaerobic growth which can worsen the condition and result in sepsis.

Signs and symptoms: Acute abdomen and fever with tachycardia and toxic symptoms and sepsis. 10–15% can result in rupture and would require urgent exploration.

The treatment would be as mentioned in the table but with close vigilance for deterioration and if no change in status to consider surgical drainage.

- Laparoscopy or exploratory laparotomy be used to drain pelvic abscesses and do adhesiolysis in order to hasten the disease's early resolution.
- Sometimes a less intrusive but as effective, an ultrasound-guided aspiration of pelvic fluid collection may be suggested.

β-lactam/β-lactamase inhibitor Combinations

Although cephalosporins are generally preferred over β-lactam/β-lactamase inhibitor combinations for treating extended-spectrum-lactamase producers, doing so may prevent the spread of these latter pathogens as well as other resistant pathogens like *Clostridium difficile* and vancomycin-resistant enterococci.

Sulbactam is coupled with either cefoperazone or ampicillin.

After 3 days of therapy, more patients in the amoxycillin/clavulanic acid group in comparison to the triple combination group (oral ampicillin, intramuscular gentamicin, and metronidazole tablets/pessaries) demonstrated a reduction in pain and discharge symptoms (p 0.05).

It is advised that patients who are hospitalised with severe PID and/or tubo-ovarian abscess be released after completing a 14-day course of broad-spectrum oral antibiotics. The most often suggested methods for getting rid of these organisms are:

1. Amoxicillin and clavulanic acid, 2–3 g/day + doxycycline (200 mg/day)
2. Amoxicillin and clavulanic acid 2–3 g/ day + ofloxacin (400 mg/day)

Table 36.5 shows drugs, pharmacokinetics, side effects and contraindications.[20–25]

CONCLUSION

PID is a disease which has high implications for future fertility and well-being. The prevention with safe sexual practices has to be promoted and emphasized on, however aggressive primary treatment is a must to prevent or reduce the sequalae. There is a need for treatment that targets the broad-spectrum of organisms that may be responsible for the issue at hand. The World Health Organization (WHO) has recognized syndromic case management (SCM), a comprehensive strategy for STI/RTI control, as the cornerstone of STI/RTI management. The treatment techniques include a careful follow-up program for each patient, contact tracing, and partner therapy to stop the disease from spreading. The implementation of treatment and prevention methods at the individual level is just as crucial as it is at the social and governmental levels. Young women must be safeguarded against STI/RTI and pregnancy due to the high prevalence of unprotected sexual activity among adolescents. Every chance to inform, prevent, and treat STI/RTI should be taken, especially when young women are seeking abortion treatment, pregnancy care, or assistance with any gynecological disorders.

Table 36.5: Drugs for PID with their pharmacokinetics, side effects and contraindications

Name and spectrum of coverage	*Pharmacokinetics*	*Side effects*	*Contraindications*
Cephalosporins, grouped into five generations Gram-positive and gram-negative bacteria Third Generation • Cefonicid • Cefotetan • Ceftriaxone Others: Cefoparazone, cefmenoxime, ceftriaxone, cefbuperazone, and latamoxef Bactericidal	Third generation—eliminated rapidly, serum half-lives—1 to 2 hours. Third generation have to be given IV or IM • $t_{1/2}$ of 4.4 hours • $t_{1/2}$ of 3.5 hours • $t_{1/2}$ of 8.5 hours Eliminated mostly by the kidneys, high biliary elimination Predominant excretion-bile/faeces (44% of dose)	Abdominal pain, diarrhoea, nausea and vomiting, decreased appetite Injection site inflammation or skin rash Leukopenia, Thrombocytopenia Swelling of tongue and throat and difficulty in breathing *Serious side effects:* Major hypersensitivity Drug-induced immune hemolytic anemia (DIIHA) Pseudomembranous colitis Suppression of gut flora causing reduction in vitamin-K synthesis Bleeding Disulfiram-like reaction	Known allergy to the cephalosporin group of antibiotics, allergic reactions in 10% of patients with known allergies to penicillins. Cephalosporins with warfarin, combination, correlates with an increased risk of bleeding. As a precautionary measure, patients should avoid alcohol consumption while on third-generation agents to avert disulfiram-like reactions. Pregnancy category B medications—not CI in pregnancy and compatible with breastfeeding.
Azithromycin Broad-spectrum macrolide antibiotic Bacteriostatic *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae, Chlamydophila pneumoniae, Mycoplasma pneumoniae* *Chlamydia trachomatis* or *Neisseria gonorrhoeae* *Haemophilus ducreyi*	Long half-life—68 hours and a high degree of tissue penetration, additional immunomodulatory effects[17] 37% is bio available after oral administration and absorption is not affected by food. Predominant excretion—bile/faeces	Common—vomiting and diarrhoea, reducing its absorption further. Serious—major adverse effects include cardiovascular arrhythmias, hepatotoxicity and caution for patients with renal GFR <10 ml/min	It comes under pregnancy category B drug. Single high dose or short course over 3 days is more effective with better bacterial clearance then same total dose over longer periods, but side effects have to be kept in mind
Metronidazole Antibiotic and antiprotozoal medication, effective against anaerobic infections	Orally absorption almost complete, with >90% bioavailability for tablets. Rectal and intravaginal absorption are 67 to 82%, and 20 to 56%.	Primary adverse effects of metronidazole include confusion, peripheral neuropathy, metallic taste, nausea, vomiting, and diarrhoea.	Documented hypersensitivity to the drug or its components, avoided in first-trimester pregnancy.

(*Contd...*)

Table 36.5: Drugs for PID with their pharmacokinetics, side effects and contraindications (*Contd...*)

Name and spectrum of coverage	*Pharmacokinetics*	*Side effects*	*Contraindications*
Either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis. Also giardiasis, trichomoniasis, and amebiasis. Other members of this class include tinidazole, ornidazole and secnidazole. They have prolonged half-lives compared with metronidazole	Metabolized extensively by liver into 5 metabolites—hydroxy metabolite has biological activity of 30 to 65% and a longer elimination half-life than the parent compound, renal and liver diseases lead to a decreased clearance of metronidazole	Headache, vaginitis and nausea. Adverse events affecting less than 10% of the population are metallic taste, dizziness, genital pruritus, abdominal pain, diarrhoea, xerostomia, dysmenorrhea, urine abnormality, urinary tract infection, bacterial infection, candidiasis, flu-like symptoms, upper respiratory tract infection, pharyngitis, and sinusitis. Rarely, there are reports of transient leukopenia and neutropenia as well.[19,20] Comes with a black box warning that it may be carcinogenic Prolonged drug courses can causes severe neurological disturbances due to the risk of cumulative neurotoxicity, fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis.	Void consuming alcohol or products containing propylene glycol while taking metronidazole and within 3 days of therapy completion. Metronidazole is likewise contraindicated if there has been recent disulfiram use within the past 2 weeks.
Doxycycline—tetracyclines wide range of gram-positive and -negative bacteria Bacteriocidal	Completely absorbed with a bioavailability of more than 80%[20] with an average of ~95% Absorption takes place in the duodenum.[21] Food has less effect on absorption. Eliminated unchanged by both the renal and biliary routes. Bile concentrations may be 10–25 times those in serum. Slowly absorbed orally, taking 2–3 hours to reach peak concentrations.	Headaches, feeling sick, increased skin sensitive to the sun including photo-onycholysis. Oral thrush. Serious—diarrhea and blood in stools, jaundice, sore throat, ringing or buzzing in the ears, intracranial hypertension, nose bleeds.	Alcohol with doxycycline—reduces the efficacy of doxycycline, allergic reaction Kidney or liver problems, oesophagitis, have lupus or myasthenia gravis. Pregnant or breastfeeding—(small chance that it can affect teeth and bone development—seen more if babies given the drug directly rather than through breastfeeding)

(*Contd...*)

Table 36.5: Drugs for PID with their pharmacokinetics, side effects and contraindications (*Contd...*)

Name and spectrum of coverage	*Pharmacokinetics*	*Side effects*	*Contraindications*
	The elimination half-life is long, ranging from 12 to 25 Predominant excretion—urine (30–65% of dose)		
Quinolones Potent antimicrobial agents—fluoroquinolones, namely ofloxacin, ciprofloxacin, norfloxacin, pefloxacin, levofloxacin, moxifloxacin bactericidal effect against numerous pathogens including Gram-positives, gram-negatives, aerobes and anaerobes Bactericidal	Predominant excretion—urine (40–50% of dose)	Generally, very safe antibiotics Gastrointestinal reactions (nausea, dyspepsia, vomiting) and CNS reactions, such as dizziness, insomnia and headache. Confusion, weakness, loss of appetite, tremor or depression Serious side effects include tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell, ruptures or tears in the aorta, which is the main artery in the body, significant drops in blood sugar levels	Epilepsy, Marfan's syndrome, Ehlers-Danlos syndrome, QT prolongation, pre-existing CNS lesions, or CNS inflammation, or who have had a stroke. They are best avoided in the athlete population. Patients with uncorrected hypokalaemia or hypomagnesaemia patients receiving antiarrhythmic agents.

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Chapter 37

Drugs in Urinary Incontinence

• Preeti Frank Lewis • Roopali Sehgal

CLINICAL APPROACH TO URINARY INCONTINENCE

The initial evaluation of urinary incontinence includes characterizing and classifying the type of incontinence, identifying underlying conditions (*e.g.* neurologic disorder or malignancy) that may manifest as urinary incontinence, and identifying causes of incontinence.[1,2]

Historically, the diagnosis of urinary incontinence required an extensive work-up. Currently, based on the new American Urological Association (AUA) and American College of Obstetricians and Gynecologists (ACOG) guidelines, the work-up of urinary incontinence has become more streamlined.[3,4] The urethral Q-tip test has mostly been eliminated, and the 7-day bladder diary has been replaced with a 2- to 3-day diary.[5–7] Similarly, simpler and shorter forms of quality-of-life (QOL), bother, and sexual dysfunction questionnaires, specific to urinary incontinence, have been developed **(Figs 37.1–37.2)**. Cystoscopy is rarely an indication for uncomplicated urinary incontinence, and urodynamics is no longer necessary prior to treatment for simple urgency urinary incontinence, or prior to surgery for uncomplicated stress urinary incontinence.[8,9]

History Taking

The history further identifies the patient's urinary symptoms and severity.[11] Classifying the type of incontinence helps direct treatment. In a multicenter study of 300 middle-aged women with moderate incontinence, the 3 incontinence questionnaire (3IQ) had a sensitivity of 0.75 and specificity of 0.77 for identifying urgency incontinence and a sensitivity of 0.86 and specificity of 0.60 for stress urinary incontinence (SUI) **(Fig. 37.1** and **Table 37.1)**.[12]

Urinary Symptoms

Frequency, volume, severity, hesitancy, precipitating triggers, nocturia, intermittent or slow stream, incomplete emptying, continuous urine leakage, and straining to void.[13]

Stress urinary incontinence: Urine loss with increase in intra-abdominal pressure, commonly occurs during laughing, coughing, or sneezing. Urine volume lost may be small or large. There is no urge to urinate prior to the leakage.

Urgency urinary incontinence/overactive bladder: Frequent, small volume voids that may keep the patient up at night or worsen after taking a diuretic. The patient has a strong urge to void but are unable to make it to the washroom in time.

The 3 incontinence questionnaire (3IQ)

1. During the last 3 months, have you leaked urine (even a small amount)?

☐ Yes ☐ No

↓

Questionnaire completed

2. During the last 3 months, did you leak urine:
(Check all that apply)

- ☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
- ☐ When you had the urge or the feeling that you needed to empty your bladder but you could not get to the toilet fast enough?
- ☐ Without physical activity and without a sense of urgency?

3. During the last 3 months, did you leak urine *most often*:
(Check only one)

- ☐ When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
- ☐ When you had the urge or the feeling that you needed to empty your bladder but you could not get to the toilet fast enough?
- ☐ Without physical activity and without a sense of urgency?
- ☐ About equally as often with physical activity as with a sense of urgency?

Fig. 37.1: The 3 incontinence questionnaire[10]

Table 37.1: Definitions of type of urinary incontinence are based on responses to question 3:

Response to question 3	Type of incontinence
a. Most often with physical activity	Stress only or stress predominant
b. Most often with the urge to empty the bladder	Urge only or urge predominant
c. Without physical activity or sense of urgency	Other cause only or other cause predominent
d. About equally with physical activity and sense of urgency	Mixed

Overflow urinary incontinence due to detrusor muscle underactivity: Loss of urine with no warning or triggers. The volume leaked may be small or large. Loss often occurs with a change in position and/or with activity. Symptoms may also be associated with urinary frequency, urgency, and/or voiding difficulties, such as urinary hesitancy, slow flow, and nocturia. This condition may be misdiagnosed as mixed urinary incontinence, in which the evaluation of post-void residual (PVR) is important.

Overflow urinary incontinence due to urinary outlet obstruction, in patients with pelvic organ prolapse, fibroids, or pelvic surgery, is often associated with stress and/

or urgency urinary incontinence symptoms and often an intermittent or slow stream, hesitancy (difficulty getting urine stream started), and a sensation of incomplete emptying. Patients with obstruction often need to strain to pass their urine or may have pain and cramping with voiding attempts and usually describe a sense of incomplete emptying (Table 37.2).

- Changes in gait or new lower-extremity weakness,
- Cardiopulmonary or neurologic symptoms (for example, the combination of overflow urinary incontinence,
- Perineal anesthesia, and new accidental bowel leakage suggests cauda equina syndrome),
- Mental status changes,
- Recurrent documented urinary tract infections (UTIs) (three or more per year),
- Advanced pelvic organ prolapse beyond the hymen,
- Elevated PVR (>1/3 total volume),
- Long-term urinary catheterization, or difficulty passing a urinary catheter.

Systemic symptoms: Evaluate all women with incontinence for UTI, with symptoms of fever, dysuria, pelvic pain, and hematuria. Sudden onset of incontinence, women with these symptoms should have appropriate work-up and evaluation for underlying conditions. We should inquire about changes in bowel function (*e.g.* constipation and accidental bowel leakage) and symptoms of pelvic organ prolapse (something coming out per vagina) as these conditions often coexist.[14]

Alcohol and caffeine:[16] Caffeine exacerbates urinary incontinence due to its smooth muscle stimulant and diuretic effects. Although a small pilot study demonstrated reductions in urinary urgency and frequency with intake of decaffeinated compared with caffeinated drinks, meta-analyses failed to identify significant associations between caffeine and urinary incontinence.[17–19]

Voiding diaries: Can be found online. While basic diary records of frequency and volume are neither sensitive nor specific for

Table 37.2: Drugs causing urinary incontinence[15]

Drug class	*Mechanism of incontinence*
I. Drugs causing overflow incontinence	
a. Anticholinergics	
1. Antidepressants	Decreased bladder contractions with retention
2. Antipsychotics	Decreased bladder contractions with retention
3. Sedative-hypnotics	Decreased bladder contractions with retention
4. Antihistamines	Decreased bladder contractions with retention
b. Nervous system depressants	
1. Narcotics	Decreased bladder contractions with retention
2. Alcohol	Decreased bladder contractions with retention
3. Calcium channel blockers	Decreased bladder contractions with retention
4. Alpha-adrenergic agonists	Sphincter contraction with outflow obstruction
5. Beta-adrenergic blockers	Sphincter contraction with outflow obstruction
2. Drugs causing stress incontinence	
Alpha-adrenergic antagonists—sphincter relaxation with urinary leakage	
3. Drugs causing urge incontinence	
Diuretics	Contractions stimulated by high urine flow
Caffeine	Diuretic effect

determining the cause of incontinence,[20,21] they may be helpful to determine if urinary incontinence is associated with high fluid intake. In addition, they provide a measure of the severity of the problem that can be followed over time. Voiding diaries also identify the maximum bladder capacity and time interval that the woman can reasonably wait between voids, a measure used to guide bladder training.

DRUGS

Stress Urinary Incontinence

No pharmacologic therapies have been approved by the United States Food and Drug Administration (FDA) for treatment of stress incontinence in women, although multiple medications have been evaluated.[22]

Duloxetine

Mechanism of action: Duloxetine is a combined serotonin/norepinephrine reuptake inhibitor. Duloxetine exerts balanced *in vivo* reuptake inhibition of 5-hydroxytryptamine (5HT) and norepinephrine (NE) and exhibits no appreciable binding affinity for receptors of neurotransmitters. The action of duloxetine in the treatment of stress urinary incontinence is associated with reuptake inhibition of serotonin and norepinephrine at the presynaptic neuron in Onuf's nucleus of the sacral spinal cord.

Pharmacokinetics: The commercially available duloxetine capsules represent a delayed-release formulation. Under steady-state conditions, exposure to duloxetine, judged by its trough plasma concentrations, increases linearly with dose in the range from 20 mg/day to 40 mg twice daily.[23]

Duloxetine is well-absorbed following oral administration[24] with a median lag time of 2–3 hours before absorption begins. Maximal plasma concentrations (C_{max}) of duloxetine occur after 6 hours when administered in the fasted state and after 10 hours when taken with a meal.[25–30]

Duloxetine is highly bound (>90%) to human plasma proteins, binding primarily to albumin and α1-acid glycoprotein.

Duloxetine has an elimination half-life of approximately 12 hours (range 8–17 hours). Therefore, steady-state plasma concentrations are typically achieved after 3 days of dosing.

Duloxetine is a substrate of CYP1A2 and hence, coadministration of CYP1A2 inhibitors like fluvoxamine, cimetidine and quinolone antimicrobials, such as ciprofloxacin and enoxacin; since these would be expected to have similar effects on the pharmacokinetics of duloxetine, these combinations should be avoided. Contrastingly, duloxetine does not inhibit or induce CYP1A2 activity and, accordingly, duloxetine does not affect the metabolism of CYP1A2 substrates such as theophylline.

Duloxetine is both a substrate and an inhibitor of CYP2D6. Therefore, co-administration of duloxetine with other drugs that are extensively metabolized by CYP2D6, particularly if they have a narrow therapeutic index, should be approached with caution. These include certain antidepressants (*e.g.* tricyclic antidepressants such as nortriptyline, amitriptyline and imipramine), phenothiazines and type 1C antiarrhythmics (*e.g.* propafenone and flecainide). Duloxetine should not be combined with monoamine oxidase inhibitors to avoid occurrence of a 5-HT syndrome.

The commercially available duloxetine formulation has an enteric coating that resists dissolution until it reaches a segment of the gastrointestinal tract where pH exceeds 5.5.

Finally, it should be considered that numerous patients with SUI concomitantly suffer from urinary urgency, in other words, have mixed incontinence. The urgency component of mixed incontinence is mostly treated with muscarinic receptor antagonists, such as oxybutynin or tolterodine. Due to their differential modes of action, it appears plausible to apply their combination in patients with mixed incontinence.

Dosage: 20 mg/day to 40 mg twice-daily.

Adverse effects: Duloxetine has a very low anticholinergic side effect profile; adverse effects of the cardiovascular, gastrointestinal, central nervous system, such as headaches and drowsiness, and fatigue, are more common.

Serious adverse effects of duloxetine include: Suicidality, serotonin syndrome, hepatoxicity, mania, syncope, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatremia.

Common adverse effects of duloxetine include: Headache, drowsiness, fatigue, nausea, xerostomia, abdominal pain, weight loss, weakness, insomnia, dizziness, change in libido, diaphoresis, constipation, decreased appetite, tremor, diarrhoea and erectile dysfunction.

URGENCY URINARY INCONTINENCE/ OVERACTIVE BLADDER

Beta-3-adrenergic agonist drugs and antimuscarinic agents are the main options for treatment of overactive bladder (OAB) symptoms.

Beta-3-adrenergic agonists—mirabegron and vibegron—are beta-3-adrenergic receptor agonists used to treat symptoms of OAB **(Fig. 37.2)**.

Mechanism of action: They work via the sympathetic nerve pathway and stimulates beta-3 receptors, causing smooth muscle relaxation in the bladder.[31] The use of a beta-3 agonist is specific to the bladder as 97% of the beta-adrenergic receptor subtypes are the beta-3 subtype.

Mirabegron

Pharmacokinetics: Mirabegron is rapidly absorbed after oral administration, reaching maximum plasma concentration in 3–5 hours whether taken with or without food. When administered as a single daily dose of 50 mg, steady-state concentrations are usually achieved within 7 days. The compound is highly lipophilic, metabolized in the liver, and eliminated in the urine (55%) and feces (34%), mainly in unchanged form.

Dose: Mirabegron is available as extended-release daily oral tablets in doses of 25 and 50 mg.

Monotherapy: Mirabegron is available in 25 and 50 mg extended-release doses. Mirabegron monotherapy is started at 25 mg daily. Although up to 8 weeks may be required for full efficacy, the dose can be increased to 50 mg daily as quickly as 4 weeks from initiation, if patients are tolerating the drug but have inadequate symptom control.

Vibegron

Pharmacokinetics: Vibegron reaches peak plasma concentration 1–3 hours after oral administration, and constant blood concentration is achieved in 7 days of once-daily administration. It is excreted in feces and urine as unchanged drug. The plasma concentration of the drug increases in people >65 years of age and those with moderate–severe renal impairment. It does not induce or inhibit the activity of CYP2D6 and CYP3A4 enzymes, and thus drug–drug interactions with most frequently prescribed agents are limited. The elimination half-life is approximately 70 hours.[32]

Dose: Vibegron is given as a single 75 mg oral dose daily.

Adverse effects: Mirabegron is avoided in individuals with poorly controlled hypertension or who develop new hypertension while using the medication.

For both mirabegron and vibegron: Urinary retention is a potential adverse effect of antimuscarinic and beta-3-adrenergic agonists.

Other side effects: Headache, runny nose, and gastrointestinal upset, dry mouth and constipation which are often mild and rarely lead to discontinuation.

Antimuscarinics: There are seven antimuscarinic agents available in different doses and formulations: Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium, and propiverine. The pharmacokinetics and dosage of these formulations are mentioned in **Table 37.3**.

Mechanism of action: Anticholinergics dampen the amplitude of bladder contractions, improving bladder capacity and reducing involuntary detrusor contractions, urgency, and frequency. Selective anticholinergics have relatively more affinity for M2 and M3 receptors, which are the most prevalent in the bladder, reducing side effects in the other systems.

Table 37.3: Antimuscarinics and their pharmacokinetics with dosage

S.No.	*Drug*	*Pharmacokinetics*	*Dosage*
1.	Darifenacin	Peak plasma concentrations of darifenacin are achieved approximately 7 hours post oral dose. Metabolized in liver by CYP3A4; maximum 7.5 mg daily with strong CYP3A4 inhibitors	7.5–15 mg, orally, once daily (extended release)
2.	Fesoterodine	After oral administration , it is well-absorbed. It undergoes rapid and extensive hydrolysis by nonspecific plasma esterases to form its active metabolite, 5-HMT, which is responsible for its antimuscarinic activity. No accumulation occurs after multiple-dose administration.	4–8 mg, orally, once daily (extended release)
3.	Oxybutynin		
	Immediate release		5 mg, orally, twice a day, four times a day
	Extended release		5–30 mg, orally, daily
	Transdermal gel (sachet)/pump		Apply 1 sachet /1 pump once daily (each delivers 1 g of gel = 100 mg oxybutynin
	Transdermal patch		Apply 1 patch, twice per week (*i.e.* once every 3 to 4 days)
4.	Solifenacin	Solifenacin undergoes hepatic metabolism and has a long half-life of 45–68 hours.	5–10 mg, orally, once a day
5.	Tolterodine	Tolterodine undergoes hepatic metabolism following oral ingestion	
	Extended release		2–4 mg, orally, once a day
	Immediate release		1–2 mg, orally, once a day
6.	Trospium	After oral administration, less than 10% of the dose is absorbed. Peak plasma concentrations (C_{max}) occur between 5 and 6 hours post-dose.	
	Extended release		60 mg, orally, once daily
	Immediate release		20–40 mg orally, once daily
7.	Propiverine		30 mg, orally, daily

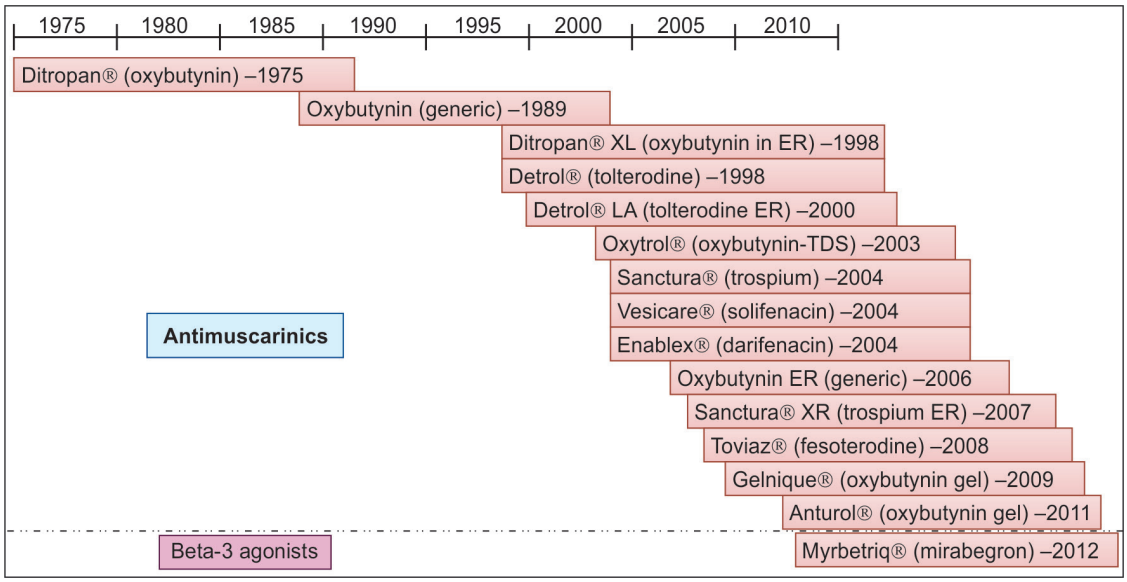
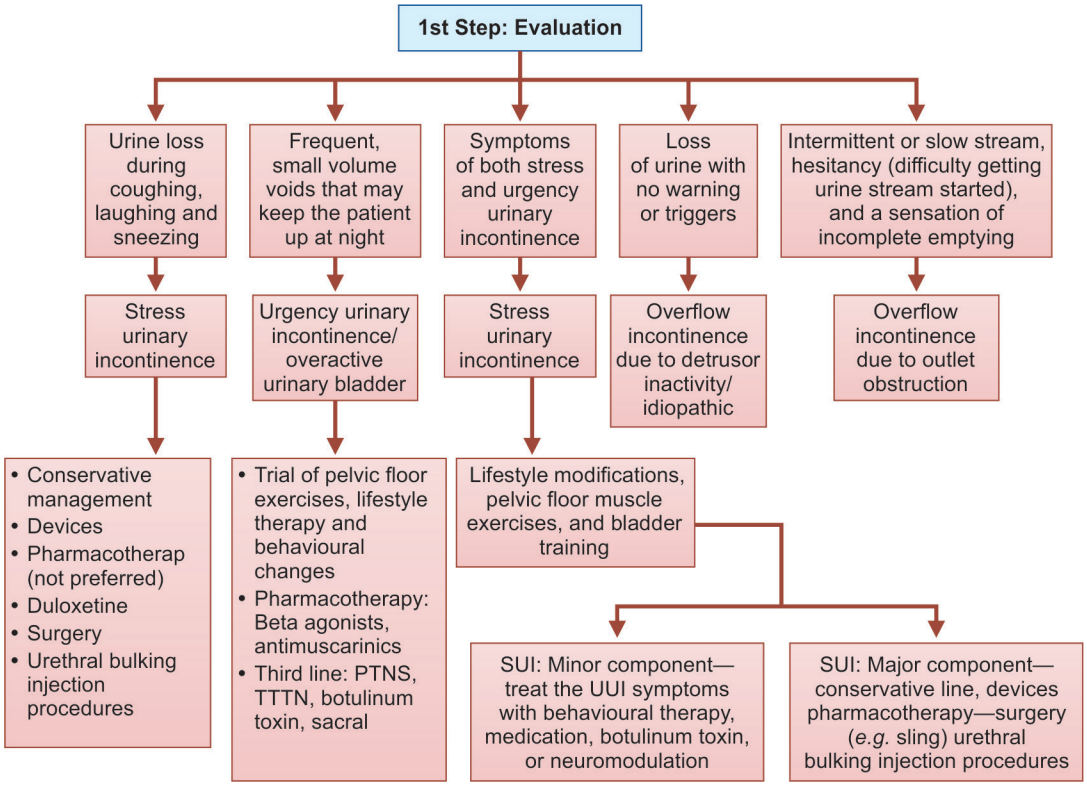
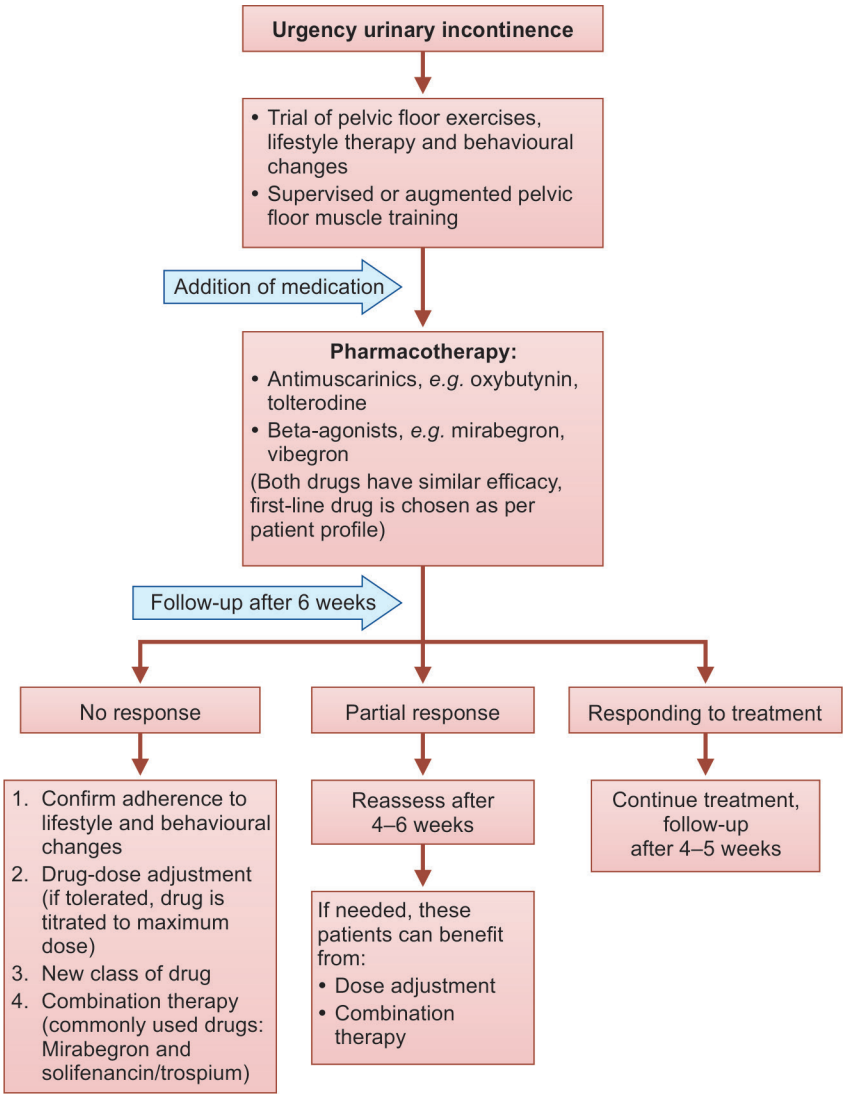


Fig. 37.2: History of OAB medications FDA approvals[33]

Flowchart 37.1: Evaluation of urinary incontinence



Flowchart 37.2: Approach to urge incontinence



Adverse Effects of Antimuscarinic Drugs

Dry mouth with difficulty in swallowing, thirst, dilatation of the pupils with difficulty accommodating and sensitivity to light, *i.e.* blurred vision, increased intraocular pressure, hot, dry and flushed skin, bradycardia followed by tachycardia, palpitations and arrhythmias, difficulty with micturition—urinary retention and constipation.

More rarely: Fever, confusion, mania, hallucinations and rashes.

Combination therapy: Options for combination therapy include use of a beta-3 adrenergic agonist plus an antimuscarinic drug or two antimuscarinic drugs together.

Combined antimuscarinic and beta-3-adrenergic agonist: Combination antimuscarinic and beta-3-agonist treatment is helpful for patients with persistent symptoms who are unable to increase the dose of the initial medication dose secondary to side effects or dose limits.

Dual antimuscarinic therapy: Dual antimuscarinic therapy may be helpful in those patients with OAB who have a partial but inadequate response to single-agent treatment and are unable to access beta-3-adrenergic agonist medications.

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Chapter 38

Drugs in Vaginal Discharge

• Tejal Poddar • Mandakini Megh

Introduction

Vaginal discharge may be a complaint or a finding on examination. Patients may complain of excessive secretions, colored or textured discharge. Physiologic discharge should be differentiated from abnormal discharge.

Psychosexual problems may present with recurrent episodes of vaginal discharge and vulval burning. It needs to be considered if tests for specific infections are negative. Many of the symptoms and signs are non-specific and allergic and irritant reactions or vulval dermatoses should be ruled out.

Definition

Abnormal vaginal discharge is defined as discharge that is different from normal with respect to consistency/colour/odour/(*e.g.* discoloured or purulent or odorous).

Abnormal discharge is often associated with pain during intercourse (dyspareunia), or painful or difficult urination (dysuria) or lower abdominal pain or vulval pruritis.

CAUSES OF VAGINAL DISCHARGE

Vaginal discharge may be caused by a number of physiological and pathological conditions (Table 38.1).

VAGINITIS

Abnormal vaginal discharge is most often associated with infection.

Important causes are: Bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) or trichomoniasis vaginalis (TV).[1] BV is one of

Table 38.1: Types of vaginal discharge

Physiological	*Pathological*
Ovulation	Vaginitis
Premenstrual phase	Sexually transmitted diseases
During and after intercourse	Cervical: Erosion, ulcer, polyp and ectropion
During pregnancy	Genital prolapse with ulcer
During puerperium	Foreign body
	Malignancy
	Atrophic vaginitis
	Pyometra

the most common and accounts for up to 50% of all infections.[2,3]

Pathogenesis

In women of reproductive age, *Lactobacillus* species is one of the predominant constituents of normal vaginal flora. Vaginal pH is maintained in the normal range by colonization by these bacteria (3.8 to 4.2), thereby preventing overgrowth of pathogenic bacteria.

Factors that predispose to overgrowth of bacterial vaginal pathogens include:

- Use of antibiotics (may decrease lactobacilli)
- Alkaline vaginal pH due to menstrual blood or semen
- Vaginal douching
- Pregnancy
- Diabetes mellitus
- An intravaginal foreign body (*e.g.* a forgotten tampon or vaginal pessary)

Etiology and Transmission

Bacterial Vaginosis

Bacterial vaginosis (BV) is the one of the most common causes of abnormal vaginal discharge in woman of childbearing age, but may also be encountered in menopausal women, and is rare in children.[4]

BV represents a change in the normal microbiome of the vagina with an overgrowth of facultative anaerobic organisms, hence bacterial vaginosis is not a true infectious or inflammatory state (*e.g. Gardnerella vaginalis*, *Bacteroides* species, *Peptostreptococcus* species, *Fusobacterium* species, *Prevotella* species, and *Atopobium vaginae*).[5,6]

BV can arise and remit spontaneously. Although not strictly considered a sexually transmitted infection (STI), it is associated with sexual activity. The exact cause of BV is still unclear but evidence suggests that formation of a biofilm with *G. vaginalis* is important in the switch from normal vaginal flora to BV **(Fig. 38.1)**.[7,8]

Candidiasis

Candidiasis is one of the most prevalent form of vaginitis. An estimated three-fourths of women will experience at least one symptomatic episode during their lifetime and 10% will experience chronic recurrent vulvovaginal candidiasis (at least four episodes per year). Vulvovaginal candidiasis results from an overgrowth of *Candida albicans* in 90% of women (remainder with other species, *e.g. Candida glabrata*).[9,10]

More than 60% of healthy premenopausal women are colonised with *Candida*, with higher rates in pregnancy, and lower rates in children and postmenopausal women without hormonal replacement therapy.[11,12]

Predisposing factors include: Endogenous or exogenous immunosuppression (including diabetes mellitus and immunosuppressive

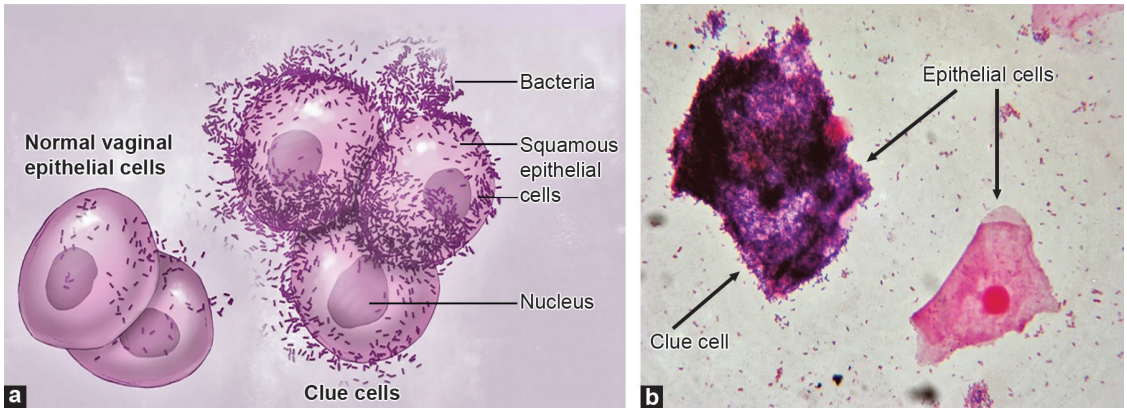

Fig. 38.1: Histopathology of bacterial vaginosis

medication) antibiotic therapy, pregnancy, *Candida albicans* visualized by Gram stain and microscopy.

Trichomoniasis Vaginalis

Trichomonas vaginalis (TV) is a flagellated protozoan that is a parasite of the genital tract. It is almost exclusively sexually transmitted. Due to specificity of site, infections follows intravaginal or intraurethral inoculation of the organism. In women, urethral infection is present in 90% of episodes, although the urinary tract is the sole site of infection in 5% of cases.

Predisposing factors are multiple sexual contacts, unhygienic conditions and infected partner **(Fig. 38.2)**.

Complications

Bacterial vaginosis (BV) is a risk factor for preterm birth and low-birth weight. However, prospective treatment studies have yielded inconsistent results as to the benefit of screening and treating for bacterial vaginosis in pregnancy. Gynecologic complications include postoperative infections following gynecologic surgery; acquisition of sexually transmitted diseases, including pelvic inflammatory disease; acquisition and transmission of human immunodeficiency virus (HIV); and recurrent urinary tract infections. Screening and treating for bacterial vaginosis prior to elective gynecologic procedures are recommended. Trichomoniasis has also been associated with preterm birth and acquisition and transmission of HIV.

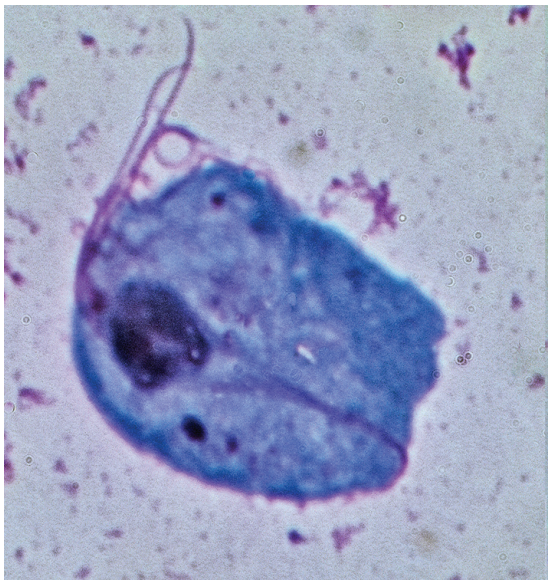

Fig. 38.2: *Trichomonas vaginalis*. May-Grünwald staining

Symptoms and Signs

There are most common symptoms and signs of vaginal infections, but these are frequently absent or non-specific.[13,14] The diagnosis of both BV and candidiasis based on clinical symptoms and signs supported by laboratory findings, which themselves vary in specificity and sensitivity. **Box 38.1** shows symptoms associated with the common causes of vaginal discharge. **Table 38.2** shows the type of discharge as per BV, TV, candidiasis and genital ulcer.

Box 38.1: Symptoms associated with the common causes of vaginal discharge[15,16]

The following findings are the alert signals of concern:

- Pelvic pain of fever
- Postmenopausal women with bloody discharge
- Fecal discharge (suggesting a fistula, even if not seen)
- Trichomonal vaginitis in children (suggesting sexual abuse)

Table 38.2: Conditional types of discharge in BV, TV, candidiasis and genital ulcer

Condition	*Type of discharge*
Normal	White or clear, odorless, and nonirritating
Bacterial vaginosis	Thin, gray discharge with a fishy odour
Trichomoniasis vaginosis	Yellow-green vaginal discharge, often with a fishy odour, frothy
Candidiasis	Cottage cheese like white discharge
Genital ulcer	Bloody or watery discharge

Diagnosis (Table 38.3)

Testing

Patients with vaginal itching or discharge need the following testing:

- Wet mount
- pH (Table 38.4)
- Potassium hydroxide (KOH) preparation

Vaginal secretions are tested using pH paper with 0.2 intervals from pH 4.0 to 6.0. Then, a cotton swab is used to place secretions on 2 slides; secretions are diluted with 0.9% sodium chloride on one slide (saline wet mount) and with 10% KOH on the other (KOH preparation).

The KOH preparation is sniffed (whiff test) for a fishy odor, which results from amines produced in trichomonal vaginitis and bacterial vaginosis. The slide is examined using a microscope; KOH dissolves most cellular material except yeast hyphae, making identification easier. The saline wet mount is examined using a microscope as soon as possible to look for clue cells and motile trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation. If clinical criteria and in-office test results are inconclusive, the discharge may be cultured for fungi and trichomonads.

Treatment (Table 38.5, Boxes 38.2 and 38.3)

Treatment of Vaginal Itching and Discharge

- Causes of vaginal pruritus and itching—age dependent.

Table 38.3: Diagnosis of BV, TV and candidiasis[13]

Criteria	*Bacterial vaginosis*	*Trichomoniasis*	*Candidiasis*
Vaginal pH	>4.5	All pH	>4.5
Saline microscopy of vaginal discharge from lateral vaginal wall	Clue cells (95% of cases)	Pseudohyphae (40–60% cases), blastospores (addition of KOH to the wet smear (40–80% cases) lyses epithelial cells and may make hyphae more apparent)	Flagellated protozoa
Gram stain of vaginal discharge from lateral vaginal wall		Spores/pseudohyphae (65% or more of symptomatic cases)	
Whiff test—release of fishy odour on adding alkali (10% KOH)	Positive	Negative	Usually positive

Table 38.4: Use of vaginal pH in diagnosis[13]

3.5	*4.0*	*4.5*	*5.0*	*5.5*	*6.0*
The normal vaginal pH remains between 3.8 and 4.5. An altered vaginal pH is indicative of vaginal infection.					
pH	≤4.5	<4.5	>4.5	≥5.0	
Vaginal discharge	+/–	+ (white, thick, clumpy discharge)	+ (white/grey, thin, clumpy discharge)	+ (greenish-yellow, frothy discharge)	
Malodour	–	–	+	+	
Itching	–	+	–	+	
Burning	–	+	–	–	
	Normal	Candidiasis	Bacterial vaginosis	Trichomoniasis	

Box 38.2: Recommended topical treatment regimens for vulvovaginal candidiasis[20]

Over-the-counter intravaginal agents

- Clotrimazole, 1% cream, 5 g, intravaginally, daily for 7 to 14 days
- Clotrimazole, 2% cream, 5 g, intravaginally, daily for 3 days
- Miconazole, 2% cream, 5 g, intravaginally, daily for 7 days
- Miconazole, 4% cream, 5 g, intravaginally, daily for 7 days
- Miconazole, 100 mg, vaginal suppository, one suppository daily for 7 days
- Miconazole, 200 mg, vaginal suppository, one suppository daily for 3 days
- Miconazole, 1,200 mg, vaginal suppository, one suppository for 1 day
- Tioconazole, 6.5% ointment, 5 g, intravaginally in a single application

Prescribed intravaginal agents

- Butoconazole, 2% cream, 5 g, intravaginally in a single application
- Terconazole, 0.4% cream, 5 g, intravaginally, daily for 7 days
- Terconazole, 0.8% cream, 5 g, intravaginally, daily for 3 days
- Terconazole, 80 mg, vaginal suppository, one suppository daily for 3 days
- Fenticonazole, 600 mg, single dose vaginally; 300 mg, vaginally on day 1 and day 3
- Itraconazole, 200 mg, orally, twice a day for 1 day

Box 38.3: Treatment recommendations for vaginal dryness

- Topical estrogen therapies reverse these mucosal changes and are effective treatments for the symptoms of atrophic vaginitis.[14]
- Vaginal moisturizers and lubricants also provide symptomatic relief for vaginal dryness and dyspareunia, respectively.[14]
- Probiotics help reduce vaginal discharge, odor and prevent bacterial vaginosis and complicated vulvovaginal candidiasis.[16]
- Topical vaginal preparation containing hyaluronic acid may improve symptoms of vaginal dryness in vulvovaginal atrophy.[15]
- Isoflavone containing vaginal gel may provide relief of vaginal dryness and dyspareunia.[20]

- Measure vaginal pH and obtain a sample of secretions for microscopic examination and testing;
- If needed, do testing for sexually transmitted infections.
- In postmenopausal women, promptly evaluate any vaginal discharge.

Cervicitis may be difficult to diagnose. When in doubt, offer treatment for cervicitis to women with vaginal discharge and any of the these risk factors:

- Urethral discharge in the partner
- Context of sexual violence or prostitution
- New partner or more than one partner in the preceding 3 months.

Methods for Diagnosis of Vaginal pH

1. Litmus paper
2. Gloves.[12]

Differential Diagnosis[9]

- Vaginal infection
- Bacterial vaginosis
- Candidiasis
- Trichomoniasis.

Bacterial Vaginosis

The primary treatment of bacterial vaginosis is oral metronidazole 400 mg given thrice a day for 7 days.[18]

The cure rate after treatment with metronidazole is up to 95%, but after 4 weeks this declines to 80% in open-label studies and less than 70% in blinded studies.[17]

A single 2.0 g dose of metronidazole in treating trichomoniasis is less effective and is not recommended.[19] Vaginal preparations containing 0.75% metronidazole gel or 2% clindamycin cream or ovules containing 100 mg, clindamycin; OD are effective and have few systemic effects.[19]

Trichomoniasis

Metronidazole, 2 g, orally, single or divided dose on the same day or tinidazole, 2 g, orally, single dose.

Table 38.5: Treatment of BV and TV

Initial regimens	*Alternative regimens*	*Pregnancy*	*Recurrence*	*Treatment of sex partners*
Bacterial vaginosis				
Metronidazole, 400 mg, orally, thrice daily for 7 days* or Metronidazole, 0.75% gel, one full applicator (5 g), intravaginally, daily for 5 days or Clindamycin 2% cream, one full applicator (5 g), intravaginally, at bedtime for 7 days	Tinidazole, 2 g, orally, once daily for 2 days or Tinidazole, 1 g, orally, once daily for 5 days or Clindamycin, 300 mg, orally, twice daily for 7 days or Clindamycin, 100 mg, intravaginally, at bedtime for 3 days	Metronidazole, 400 mg, orally, thrice daily for 7 days	First recurrence: Retrial of same regimen or Trial of alternative initial regimen Multiple recurrences: Metronidazole, 0.75% gel, intravaginally, twice weekly for 4 to 6 months	Routine treatment of sex partners is not recommended
Trichomoniasis				
Metronidazole, 2 g, orally, single or divided dose on the same day or Tinidazole, 2 g, orally, single dose	Metronidazole, 400 mg, orally, thrice daily for 7 days	Metronidazole, 2 g, orally, single dose in any stage of pregnancy	Differentiate persistent or recurrent infection from reinfection[11] If metronidazole, 2 g, single dose fails: Trial of metronidazole 400 mg, thrice daily for 7 days If metronidazole 400 mg thrice daily for 7 days fails: Trial of metronidazole, 2 g, daily for 7 days If above regimens fail: Consider susceptibility testing	Concurrent treatment of sex partners is recommended Advise refraining from intercourse until partners are treated and symptom-free

In the case of treatment failure: Tinidazole, PO, 500 mg, 2 times daily for 5 days or metronidazole, PO, 400 to 500 mg, 2 times daily for 7 days.

Vulvovaginal Candidiasis

Clotrimazole (500 mg, vaginal tab.), 1 tablet inserted deep into the vagina at bedtime, single dose.

If the patient has extensive vulvar involvement, miconazole, 2% cream (one application to the vulva, 2 times, daily for 7 days), may be used in combination with the intravaginal treatment above. Miconazole cream may complement, but does not replace, treatment with clotrimazole.

Treatment of the Partner

When the patient is treated for vaginitis or cervicitis, the partner receives the same treatment as the patient, whether or not symptoms are present.

In the case of vulvovaginal candidiasis, the partner is treated only if symptomatic (itching and redness of the glans/prepuce): Miconazole, 2% cream, one application, 2 times daily for 7 days, pessaries PV, twice daily for 10 days.

Role of Probiotics

Antimicrobial therapy is generally effective, but there is still a high incidence of recurrence and increase of resistance. Thus, it is suggested that administration of probiotics using selected *Lactobacillus* strains can be an effective strategy for preventing vaginal infections.[20]

Probiotics:

- Have positive effects on vaginal microflora composition by promoting the proliferation of beneficial microorganisms
- Alter the intravaginal microbiota composition
- Prevent vaginal infections in postmenopausal
- Reduce the symptoms of vaginal infections and prevent vaginitis.

The use of *Lactobacillus acidophilus, Lactobacillus rhamnosus GR-1 and Lactobacillus fermentum RC-14* at a dose of at least 10 CFU/day for 2 months is found to be effective.[21]

In a Cochrane analysis, the efficacy and safety of probiotics administered intravaginally combined with antibiotic therapy for the treatment of bacterial vaginosis is established. Antibiotics can break down the overgrowth of vaginal anaerobes and formation of biofilm. Hence, probiotics administered intravaginally will adhere to and colonize vaginal epithelial cell surfaces.[22]

A Cochrane analysis, suggests beneficial outcome of microbiological cure with the oral metronidazole/probiotic regimen and the probiotic/estriol preparation.[23,24]

Summary

Vaginitis is an overgrowth of anaerobic organisms (*e.g. Gardnerella vaginalis, Mycoplasma hominis, Mobiluncus* spp.) in the vagina leading to a replacement of lactobacilli and an increase in vaginal pH.

Signs and Symptoms

For bacterial vaginosis: Fishy odor; thin, off-white homogenous discharge that may worsen after intercourse; pelvic discomfort without inflammation.

For vulvovaginal candidiasis: White, thick, cheesy, or curdy discharge; vulvar itching or burning; no odor (pruritis dysuria), vulvar erythema and edema.

For trichomoniasis: Green or yellow, frothy discharge; foul odor; vaginal pain or soreness copious, malodorous, yellow-green (or discolored) discharge, pruritus vaginal irritation. No symptoms with inflammation and strawberry cervix.

Screening and Diagnosis

- Screening of asymptomatic patients for trichomoniasis is not recommended.
- Culture for the diagnosis of bacterial vaginosis not needed because it represents a polymicrobial infection.
- Nucleic acid amplification testing is recommended for the diagnosis of trichomoniasis in symptomatic or high-risk women.
- Elevated vaginal pH in the absence of current vaginal infection is a risk for adverse pregnancy outcome that is mediated by systemic inflammatory response.

Treatment

- It is recommended to screening for increased vaginal pH during pregnancy, as it may be useful in reducing preterm birth rates.
- Vaginally administered probiotics affects vaginal microflora composition by promoting the proliferation of beneficial microorganisms, alters the intravaginal microbiota composition and prevents vaginal infections. Probiotics also reduce the symptoms of vaginal infections such as vaginal discharge, odor, etc. and are helpful for the treatment and prevention of bacterial vaginosis and complicated vulvovaginal candidiasis.
- Hyaluronic acid, vaginal gel and estriol cream can significantly improve the clinical symptoms of vaginal dryness.
- Moisturizers help maintain natural secretions and coital comfort. The length of effectiveness is generally less than 24 hours.
- *Vaginal dryness:* Topical estrogen replacement therapies reverse these mucosal changes and are effective treatments for the symptoms of atrophic vaginitis:
  - Vaginal moisturizers and lubricants also provide symptomatic relief for vaginal dryness and dyspareunia, respectively
  - Vaginally administered probiotics help reduce vaginal discharge, odor, etc. and prevent bacterial vaginosis and complicated vulvovaginal candidiasis
  - Topical vaginal preparation containing hyaluronic acid, improves vaginal dryness in vulvovaginal atrophy.
  - Isoflavone containing vaginal gel provides relief of vaginal dryness and dyspareunia symptom.
- Treatment of uncomplicated vulvovaginal candidiasis involves a short course of antifungals; oral and topical preparations are similarly effective
- Treatment of complicated vulvovaginal candidiasis involves an intensive, longer course of antifungals
- Vaginally administered probiotics containing *L. brevis CD2*, *L. salivarius subsp*. salicinius, L. plantarum can cure bacterial infection and reduce vaginal inflammatory response
- For non-infectious vaginitis topical vaginal estrogen is preferred because of the low systemic absorption and reduced risk of adverse effects compared with oral therapy. Estrogen-containing creams, pessaries, intravaginal tablets and the estradiol vaginal ring appear equally effective for the symptoms of atrophic vaginitis
- First-line nonhormonal treatment recommendations include vaginal lubricants and moisturizers; continued sexual activity should be encouraged
- Antibiotics, such as amoxicillin/clavulanic acid, are shown to be effective in women with anaerobic vaginal isolates
- Post-infection vaginal probiotic pessaries for the treatment of bacterial vaginosis is an effective treatment for treating vaginitis
- The exogenous strains of lactobacilli have been suggested as a means of re-establishing a normal healthy vaginal flora
- In women with manifest clinical signs of bacterial vaginosis or yeast vaginitis, vaginal probiotics given in combination with antibiotic or antimycotic therapy, lowered clinical symptoms and led to lower Nugent scores compared with a treatment with antibiotics/antimycotics alone.
- Vaginal probiotics containing lactobacilli enables successfully establish normal vaginal flora in pregnant women with imbalance in vaginal flora.
- In pregnant women requiring vaginal probiotics along with antifungal or antibiotic therapy, attain normal vaginal flora and reduces inflammation after 10 days of therapy
- Vaginal lactobacilli tablet containing at least 1 billion viable lactobacilli (*L. brevis CD2*, *L. salivarius* subsp., *salicinius*

and *L. plantarum*) is effective, safe and well-tolerated in reducing the symptoms of vaginal infections and restoring the vaginal flora to normal.

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Chapter
39

Drug Therapy in Adolescent Polycystic Ovary Syndrome

• Nidhi Shah • Usha Saraiya

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of reproductive age group with a higher prevalence in adolescent girls ranging from 9% (regular cycles) to 45% (girls with oligomenorrhea).[1]

Strict criteria have been proposed to diagnose PCOS in adolescents.[2] Pathophysiology of PCOS is complex **(Fig. 39.1, Flowchart 39.1)**.

TREATMENT

The treatment for PCOS should be individualised as per the clinical picture, need and preferences of the patient.

Aim is to improve the quality of life and long-term health outcome; and may need some parental support as well as psychological counselling.

Lifestyle modification by way of diet with calorie restriction and exercise forms the first line of management of obese/overweight adolescents with PCOS.

A 5–10% reduction in weight is said to overcome menstrual irregularities, hirsutism, testosterone, sex hormone-binding globulin (SHBG) resume ovulation and fertility and regulate insulin resistance.[3]

Micronutrients, especially vitamin D has important role in treating adolescent girls with PCOS.

Pharmacotherapy for managing PCOS in adolescents includes the following:

- Inositols
- Insulin-sensitizing drugs—metformin
- Combined oral contraceptive pills
- Antiandrogens.

INOSITIOLS

Inositols are a group of natural polyols (sugars).

They are naturally present in food including fruits, like cantaloupe, grapefruit and citrus fruits, beans, whole grains and nuts, like almonds and walnuts.

Inositols form a part of the cell membrane phospholipids, plasma lipoproteins as well as the phosphate component in the nucleus; and are involved in many cellular processes, such as signal transduction, osmoregulation and ion channel regulation.

In PCOS, inositol administration:

- Improves symptoms
- Regulates the lipid levels
- Reduces testosterone and androgen levels
- Reduces appetite, fat and body mass index (BMI) via efficient breakdown of fats
- Improves insulin sensitivity
- Improves ovulation rate and menstrual cycle.[4–6]

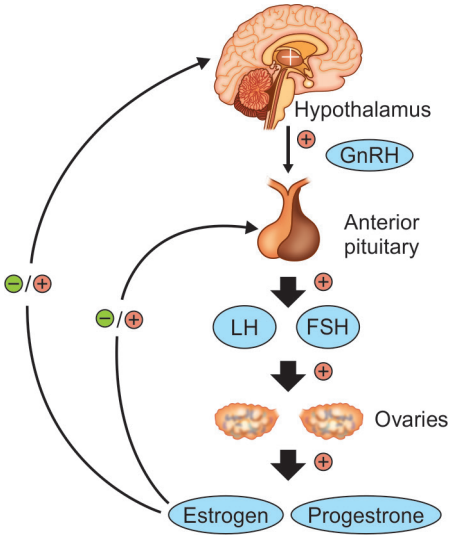
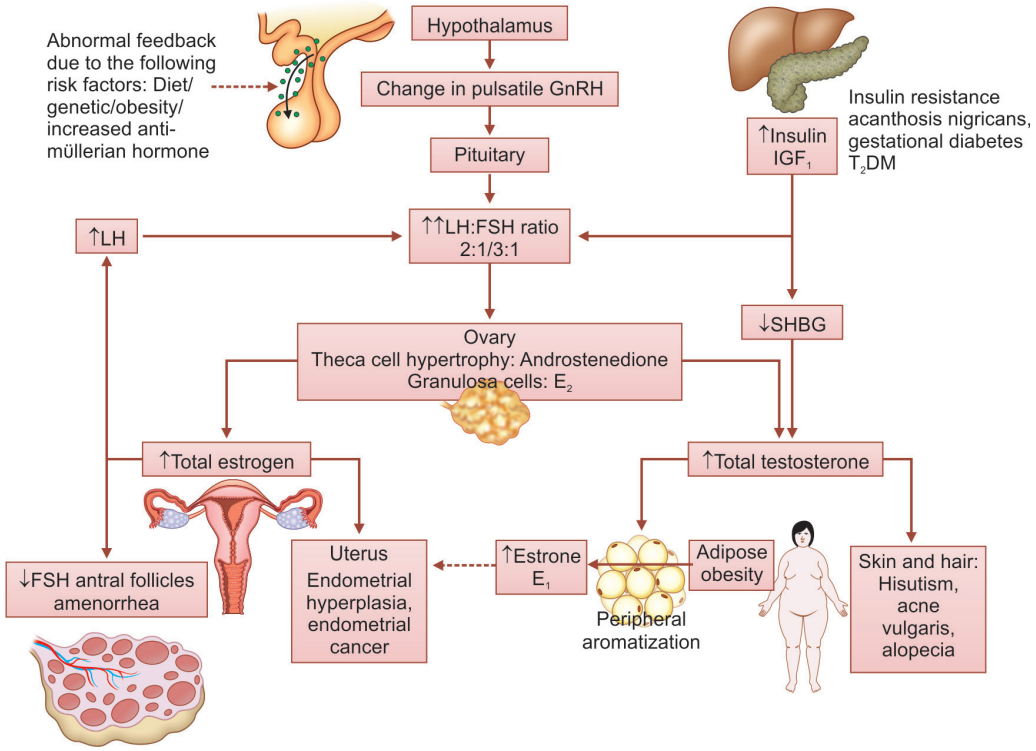


Fig. 39.1: Female HPG axis. GnRH: Gonadotropin-releasing hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone

Flowchart 39.1: Pathophysiology of PCOS. Female hypothalamic–pituitary–gonadal (HPG) axis and hypothalamic–pituitary–adrenal glands leading to androgen excess and consequently anovulation and/or metabolic disorders



PCOS: Polycystic ovary syndrome; GnRH: Gonadotropin-releasing hormone; IGF_1: Insulin-like growth factor-1; T_2DM: Type 2 diabetes mellitus; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; SHBG: Sex hormone-binding globulin

Box 39.1: International evidence-based guideline. BMC Med 2020.[2]

1. Irregular cycles defined years post-menarche; >90 days for any one cycle (>1 year post-menarche), cycles <21 or >45 days (>1 to <3 years post-menarche); cycles <21 or >35 days (>3 years post-menarche) and primary amenorrhea by age 15 or >3 years post-menarche.
2. <1 year post-menarche irregular cycles are normal pubertal transition.
3. Hyperandrogenism—hirsutism, severe acne and/or biochemical hyperandrogenaemia
4. Sonography not required for diagnosis of PCOS within 8 years post-menarche.
5. Anti-müllerian hormone not needed for PCOS diagnosis; and exclude other disorders that mimic PCOS.
6. For adolescents who have features of PCOS but do not meet diagnostic criteria, they are categorized 'at risk' and regular re-evaluations.
7. Re-evaluate them 3 years post-menarche and where only menstrual irregularity or hyperandrogenism are present initially, ultrasound can occur after 8 years of menarche.

Molecule Structure

Myoinositol (MI) constitutes 99% and D-chiro-inositol (DCI)—the remaining 1% of the total inositol amount.

Time taken to achieve **(Fig. 39.2)** maximum plasma concentration is about 4 hours.[7]

Metabolism

Excretion is via the kidneys with an elimination half-life of 5.22 hours.[8]

Dosage

Combination therapy with an MI/DCI ratio of 40:1 is recommended.[9]

Daily dosage—2 grams before breakfast and dinner for 3 months.

Mechanism of Action

Insulin resistance plays a significant role in the development of PCOS. MI and DCI are intracellularly incorporated into inositol phosphoglycans (IPGs), which are second

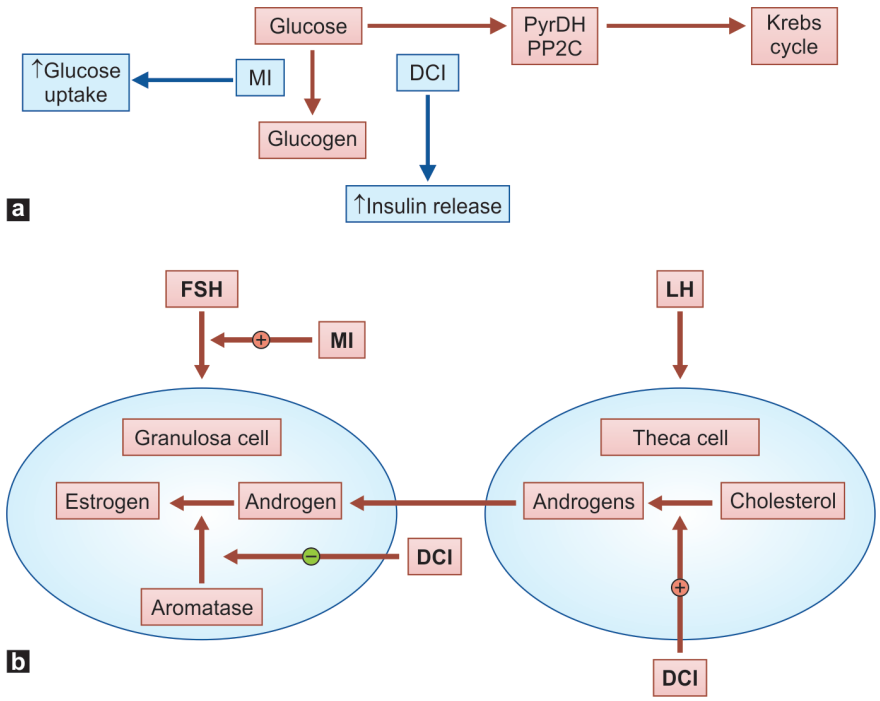


Fig. 39.2: (a) Effects of myoinositol and D-chiro-inositol on glucose metabolism in PCOS. (b) Effects of myo-inositol (MI) and D-chiro-inositol (DCI) on hormonal synthesis in PCOS.[10] FSH: Follicle-stimulating hormone; LH: Luteinizing hormone

messengers of insulin, follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH). Some actions of insulin are mediated by these IPGs.

1. Myo-inositol IPG inhibits cyclic adenosine monophosphate (AMP)-dependent protein kinase and improves glucose uptake at the cellular level.
2. D-chiro-IPG activates pyruvate dehydrogenase phosphatase and is involved in glycogen synthesis.

Under physiological conditions, the MI/DCI ratio is between 100:1 in the follicular fluid and 40:1 in plasma.[10,11]

PCOS patients have an increased DCI/MI ratio (overproduction of DCI). This in turn leads to MI deficiency in the ovary. A balance between the two inositols is associated with insulin resistance (IR) and sensitivity.

Adverse Effects

1. Gastrointestinal effects on consuming higher doses
2. Excessive DCI—↓ estrogen levels and androgen levels
3. Acne, hair loss and excessive hair growth.[11]

Metformin

It is a biguanide anti-hyperglycemic agent. In PCOS, metformin reduces androgen and serum lipid levels; induces ovulation and regularizes the menstrual cycles.

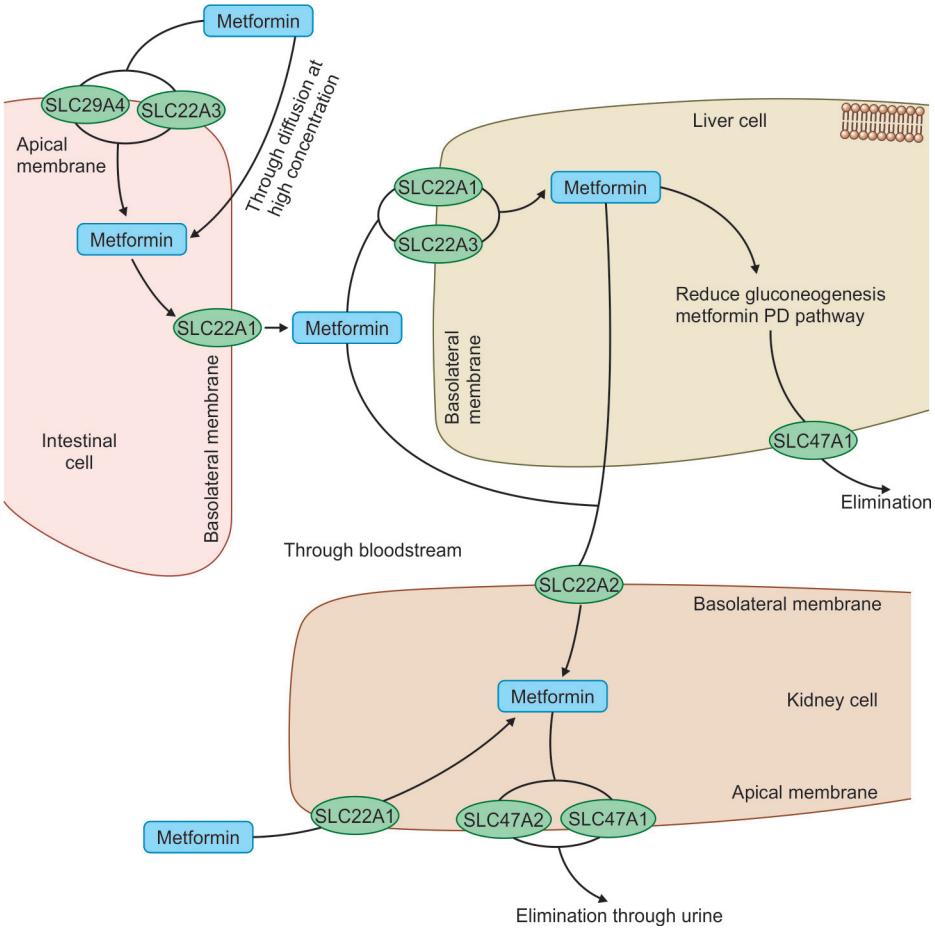


Fig. 39.3: Pharmacokinetics pathway of metformin[14]

Absorption and Bioavailability

50–60% for a 500 mg tablet taken on an empty stomach. Food reduces and delays the absorption of metformin **(Fig. 39.3)**.[12]

Distribution

Metformin is scarcely bound to plasma proteins. The plasma elimination half-life is approximately 17.6 hours, suggesting distribution within the erythrocytes.[12]

The drug is widely distributed into body tissues including the intestine, liver, and kidney.

Under routine circumstances (dosage and timing), metformin hydrochloride tablet reaches a steady-state plasma concentration within 24–48 hours, which is generally <1 µg/ml.[12]

Metabolism and Elimination

Metformin is not metabolized and 90% is primarily eliminated unchanged through the kidneys within the first 24 hours, with a half-life of approximately 6.2 hours.[12]

Dosage

Metformin hydrochloride is available as 500 mg, 850 mg and 1000 mg extended release tablets. Start with a dose of 500 mg and gradually increase by 500 mg every 1 to 2 weeks until a maximum dose of 2500/2550 mg per day is reached based on the need and tolerance of the patient.[13]

Mechanism of Action

Metformin differs from other oral anti-hyperglycemic agents; it lowers both basal and post-prandial glucose levels. It reduces hepatic glucose production by reducing gluconeogenesis, decreases intestinal absorption of glucose, reduces the synthesis of fatty acid and triglycerides, increases fatty acid β-oxidation and improves insulin sensitivity by increasing peripheral glucose uptake and utilization **(Fig. 39.4)**.[15,16]

Adverse Effects

Metformin reduces the hepatic uptake of lactate, this may increase the blood lactate levels and result lactic acidosis.[12] Risk factors for metformin-associated lactic acidosis, thus demanding cautious use is as follows:

- Impaired kidneys and liver function
- Concomitant use of drugs, like carbonic anhydrase inhibitors—topiramate
- Elderly, ≥65 years of age
- Undergoing procedures—surgery/radiological study with contrast
- Hypoxic conditions, like acute congestive heart failure
- Excessive consumption of alcohol.

Combination pills containing inositol and metformin are now available specially to treat adolescent PCOS.

Combined Oral Contraceptives (COCs) Pills

COCs are the first choice of therapy for adolescent girls with PCOS as they not only address symptoms, like menstrual irregularity (amenorrhea, oligomenorrhea, menorrhagia and abnormal uterine bleeding) and cutaneous hyperandrogenemia, but also serve as contraception in sexually-active adolescent girls.[17]

Composition

Estrogen component: Ethinyl estradiol, estradiol or estetrol.

Progesterone component: With varying degrees of androgenic and progestogenic potential **(Table 39.1)**.

- First generation progestin: Norethindrone acetate, ethynodiol acetate, lynestrenol and norethynodrel.
- Second generation progestin: Levonorgestrel, dl-norgestrel.
- Third generation progestin: Norgestimate, gestodene, desogestrel.
- Fourth generation progestin: Drospirenone and cyproterone acetate.

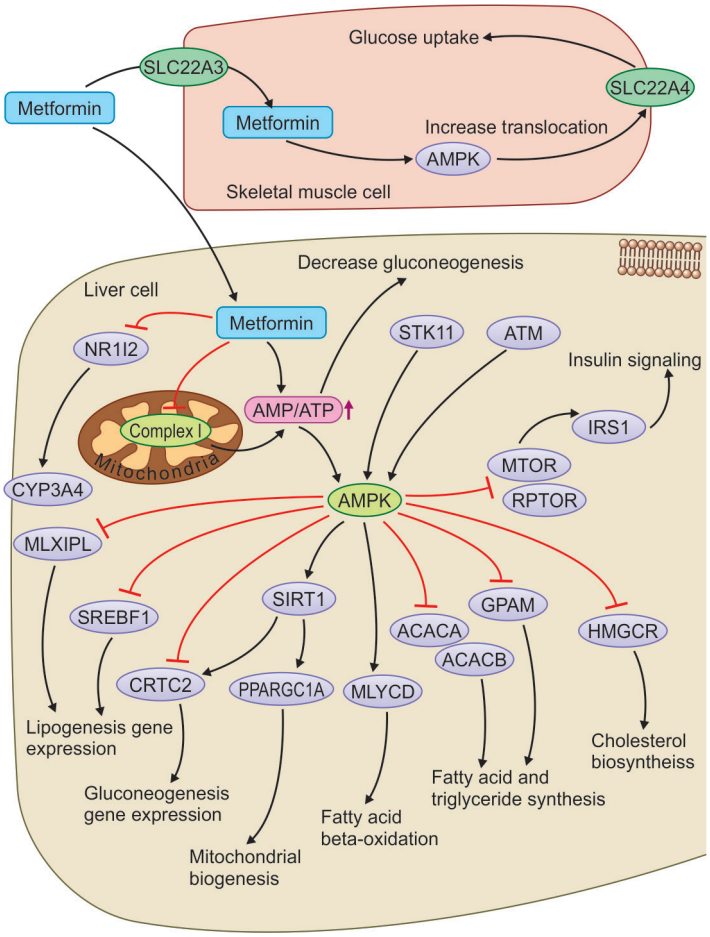


Fig. 39.4: Pharmacodynamics pathway of metformin[14]

Table 39.1: Hormonal effects produced by 4 generations of progestin[18–20]

Generation	*Progestin*	*Estrogenic*	*Progestational*	*Androgenic*
First	Norethindrone	++	++	++
	Elhynodiol diacetate	++	+++	+
	Norgestrel	–	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonoroestrel	–	++++	++++
Third	Norgestimate	–	++	++
	Desogestrel	+/–	++++	++
Fourth	Drosplrenone	–	+/-	–

+/– indicates low to no activity.
– indicates no activity.

Selection of the right combination depends on the dose required, desired effect as well as the undesirable side effects of the progestin component.[21]

Absorption, Bioavailability and Distribution

COCs are absorbed from the small intestine reaching a peak plasma level within 1–4 hours with individual variation. While levonorgestrel does not undergo first pass metabolism and has 100% bioavailability, norethisterone has an average of 70% whereas ethinyl estradiol has a mean bioavailability of 40 to 45%.[21]

COCs are bound to plasma proteins. 97–98% of ethinyl estradiol is bound to plasma albumin. The progestins are bound mainly to SHBG and to lesser extent to albumin (levonorgestrel 93 to 95%; norethisterone 79 to 80%).[21]

Metabolism

COCs are metabolized in the liver by cytochrome p450 enzymes either unchanged or by conjugation with glucuronide or sulphate; thus, drugs that induce cytochrome p450 may increase COC metabolism.

Mechanism of Action

COC reduces the androgen levels through different mechanisms:

1. COC suppress the endogenous hypothalamic–pituitary–ovarian (HPO) axis resulting in a ↓ pituitary gonadotropins thereby interfering with folliculogenesis and reducing ovarian androgen production
2. COC reduces adrenal androgen secretion and inhibits the peripheral conversion of testosterone to dihydrotestosterone as well as binding of dihydrotestosterone to androgen receptors
3. COC ↑ SHBG, thereby further reducing the free androgen index.

In addition, the progesterone component of the COC prevents unopposed action of estrogen, thereby preventing endometrial hyperplasia and menstrual irregularities.

Dosage

COC should be taken at a fixed time daily, delay of >24 hours should be avoided to ensure maximum efficacy.

COC can be prescribed as follows:

- *Cyclic:* Hormonal pills for 21–24 days, followed by 7–4 days of hormone-free pills
- *Extended cycle:* 3 months—hormone pills, followed by 1 week—placebo
- *Continuous use:* Daily usage of hormonal pills up to a maximum of 1 year.

Phases of COC

Monophasic: Start on day 1 of the cycle for 21 days—estrogen and progestin in equal proportion.

Biphasic: The estrogen level remains constant throughout the cycle with 2 different progestin levels that changes mid-cycle.

Triphasic: Varying levels of both estrogen and progestin throughout the 21 days of the cycle.

Monophasic is generally what is used in our daily practice as biphasic and triphasic pills are not well-tolerated or as effective.

Missed doses: If a patient misses a tablet, she should take the missed pill as soon as she remembers and then take her next tablet at the usual time. If she misses 2 pills in a row, she should take 2 tablets the minute she remembers as well as 2 pills the next day and then resume her routine of a pill a day.[22]

Duration of treatment with COC is not yet well-defined. Improvement in menstrual pattern is seen within 2 to 3 months. Hyperandrogenemia is also shown to improve after the third month of therapy.[21,23]

Adverse Effects[22]

Most side effects are mild and will disappear with either continued use or by switching over to another formulation.

Most common: Breakthrough bleeding and spotting.

Others: Nausea (overcome by taking the pill at bedtime), headache, abdominal cramps,

breast tenderness, ↑ vaginal discharge or libido.

Long-term serious side effects, like an ↑ in blood pressure, venous thromboembolism and breast cancer, not generally seen in adolescents.

COC does not provide protection against sexually transmitted infections.

Progestin-only Pills (POPs, Minipill)

Progestins may be used to induce a withdrawal bleed in adolescents with amenorrhea/oligomenorrhea.

Some progestin compounds have more potent antiandrogenic properties and are more effective androgenic symptoms of PCOS—hirsutism and acne.

Dosage

- Micronized progesterone (100–200 mg daily)
- Medroxyprogesterone acetate (5 mg/day)
- Norethindrone acetate (2.5 or 5 mg/day) for 5–10 days.

Contraindications[22]

Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) have set criteria for women who want to initiate COC or POP; some absolute and relative contraindications in adolescent girls are as follows:

- Cigarette smokers (>15 cigarettes/day) >35 years of age.
- Adolescents with thrombogenic mutations, like prothrombin mutation, factor V Leiden, protein C, protein S and antithrombin deficiencies
- Migraines with auras
- History of venous thromboembolism (VTE), stroke
- Valvular heart disease
- Acute liver disease/hepatocellular adenoma.

Progesterone Only Pill

- Pregnancy
- Undiagnosed abnormal uterine bleeding
- History of bariatric surgeries
- Adolescents on some antiseizure medicine.

A thorough hematological evaluation is advisable before starting COC, as menstrual irregularities may be due to thrombophilia and not hormonal imbalance.

Girls on COC should have an annual visit with their doctor for weight, BMI, blood pressure and routine medical care.

ANTIANDROGENS

Antiandrogens are a group of drugs, such as spironolactone, cyproterone acetate (CPA), or flutamide that act as competitive inhibitors of androgen-binding receptors or reduce androgen production.[24] They may be used as the first line of management for cutaneous hyperandrogenemia—acne and hirsutism.

However, these drugs have teratogenic potential and may result in feminization of the male fetus and hence, they should be administered in combination with adequate contraception in sexually active adolescent girls. In view of toxicity frequent monitoring of liver and kidney function is necessary when on antiandrogens.

CYPROTERONE ACETATE

CPA is a progestational antiandrogen. It is used along with estrogen for treating acne and hirsutism.

Absorption, Bioavailability and Distribution

When taken orally, CPA is completely absorbed with an absolute bioavailability of almost 88%.

Cyproterone acetate has a special affinity for plasma albumin with just 3.5–4%, remaining unbound.

Metabolism and Elimination

CPA is metabolised in the liver by the CYP3A4 enzyme and forms the active metabolite 15-beta-hydroxy cyproterone acetate, a metabolite with antiandrogenic activity but progestational activity.

60% is excreted in the bile and 33% through the kidney with a plasma half-life of 38 hours after oral intake.[25]

Mechanism of Action

- CPA competitively inhibits testosterone and its potent metabolite 5α-dihydrotestosterone (DHT) from binding to the androgen receptor.
- CPA may also inhibit 5α-reductase activity, decreasing the availability of the more potent androgen, dihydrotestosterone.
- It suppresses luteinizing hormone thereby reducing testosterone levels.[25]

Dosage and Follow-up

Dose: 50 to 100 mg, orally, after meals for first 10 days after a period (reverse sequence) or lower dose in combination with 20–50 µg of ethinyl estradiol.

It takes at least 6 months of treatment to notice any improvement in hirsutism with maximum effect seen after 9 to 12 months.

Adverse Effects

CPA is generally well-tolerated, but patients may complain of headache, nausea, weight gain, breast tenderness, and loss of libido. Rarely one may experience hepatic toxicity, benign or malignant hepatic tumours leading to intra-abdominal haemorrhage and thromboembolic episodes.

Contraindications

- Hepatic disease/tumours
- Patient with history of a VTE episode
- Sickle cell anaemia
- Severe chronic depression
- Past or present history of meningioma.

SPIRONOLACTONE

Spironolactone is an aldosterone antagonist with moderate antiandrogenic effects when taken in large doses, hence it is used along with COC to treat hirsutism, female pattern hair loss, and adult acne vulgaris.[26]

Mechanism of Action

1. In large doses, it is a non-selective competitive inhibitor of androgen and progesterone receptors
2. It can also inhibit 5α-reductase activity.

Dosage

Spironolactone is available as 25 mg, 50 mg, or 100 mg tablets and the dose recommended for treating acne/hirsutism is 100–200 mg daily.[27]

Adverse Reactions

Generally, well-tolerated, can occasionally cause breast discomfort, hyperkalemia, fatigue, postural hypotension, dizziness, gastrointestinal complaints and menstrual irregularities at high doses.

FLUTAMIDE

It is a nonsteroidal, selective antiandrogen without progestogenic effect. It is very effective in treating hirsutism and male pattern hair loss. The effective dose ranges from 125–500 mg daily. However, it is rarely used, as it is expensive and causes severe hepatotoxicity.[28]

CONCLUSION

PCOS is a heterogeneous endocrinopathy affecting adolescent girls. The exact etiology is unknown; however, hyperinsulinemia and hyperandrogenism form the main pathological basis of this syndrome. In adolescents, it may be difficult to differentiate irregular cycles of PCOS from physiologic anovulation. However, persistence of menstrual irregularity for >2 years post-menarche is a strong predictor of long-term ovulatory dysfunction. COC pills are the first line of medical management for menstrual disturbances and acne, metformin for weight reduction and dysglycemia and a combination of both in addition with other treatment modalities for treatment of hirsutism.

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Chapter
40

Drugs for Ovulation Induction

• Sudha Tandon • Amrita Tandon

GENERAL PHYSIOLOGY

Ovulatory dysfunction makes-up about 25% of infertility in females. For a mature oocyte to develop, it needs coordination between the hypothalamus, anterior pituitary and ovaries (hypothalamic-pitutiary axis) along with factors produced by the ovaries locally. Any disruption of this feedback mechanism can cause ovulatory dysfunction and infertility.[1]

About one million oocytes are present in the ovary at birth, and about 400–500 ovulate during the reproductive years. A single layer of granulosa cells surrounds the primordial follicles, and these are arrested in meiosis 1 until menarche.

The primordial follicle develops into the primary follicle, which then becomes the secondary follicle which is surrounded by granulosa cells containing follicle-stimulating hormone (FSH) receptors and theca cells. This stage of folliculogenesis is not dependent on gonadotropins **(Fig. 40.1)**. The majority of these preantral follicles undergo atresia. The granulosa and theca cells then proliferate and form a fluid-filled cavity called the antrum. Follicles beyond this stage are referred to as antral or pre-ovulatory follicles which are now dependent on FSH for further development.[2]

Once, the FSH threshold level is reached, a set cohort of preovulatory follicles is

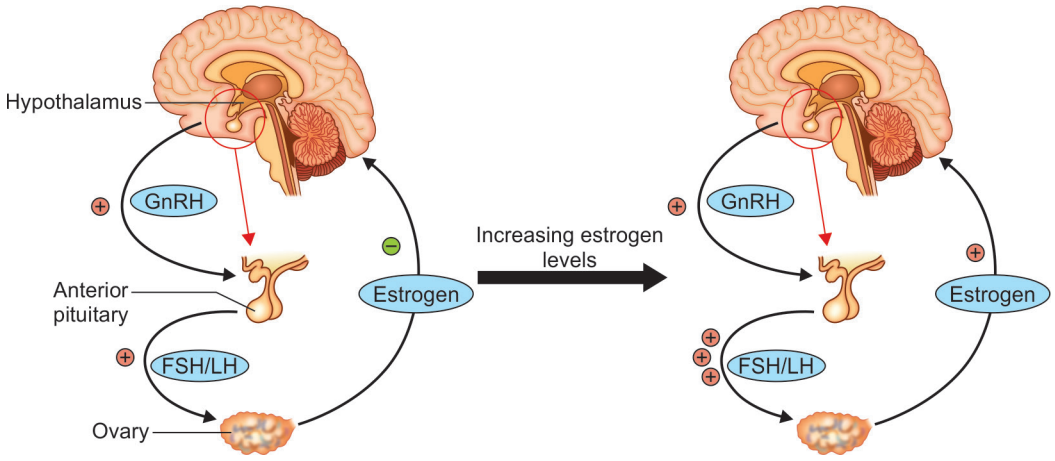

Fig. 40.1: Neural control of ovulation

Table 40.1: WHO classification of ovulatory disorders[4]

WHO Group I: Hypogonadotropic hypogonadal anovulation	5–10% of anovulatory women	Low/low-normal serum follicle-stimulating hormone (FSH) and low serum estradiol levels	Women with hypothalamic amenorrhea related to physical, nutritional, or emotional stress; weight loss; excessive exercise; anorexia nervosa and its variants; Kallmann syndrome; and isolated gonadotropin deficiency.
WHO Group II: Normogonadotropic normoestrogenic anovulation	75–85% of anovulatory women	Normal serum FSH and estradiol levels and normal or elevated LH concentrations	Polycystic ovary syndrome (PCOS)
WHO Group III: Hypergonadotropic anovulation	10–20% of anovulatory women	Elevated serum FSH and low AMH concentrations, and most have amenorrhea	Premature ovarian insufficiency
Hyperprolactinemic anovulation	5–10% of anovulatory women	Serum FSH concentrations are low or low-normal, and serum estradiol levels are usually low	

recruited. These follicles can now respond to the increasing FSH/luteinizing hormone LH levels, secrete estrogen, and grow. The dominant follicle responds more aggressively, and via aromatase, there is higher estrogen levels in the follicle's microenvironment, and large number of FSH receptors leading to follicular growth. The rest of the preovulatory follicles become atretic due to the falling FSH levels **(Fig. 40.1)**.

The theca cells produce steroids in following the LH stimulation, which then produce estrogen via aromatization. When estrogen levels peak in the circulating blood, the hypothalamus is stimulated, leading to an LH surge and thus ovulation.[3]

PRETREATMENT EVALUATION OF INFERTILITY AND OVULATORY DISORDERS[4,5]

A complete work up for infertility and endocrine dysfunction should be done in the couple before starting treatment for ovulation induction **(Table 40.1)**.

- A basic hormonal profile which includes thyroid profile (TSH), hyperprolactinemia (serum prolactin) and anti-müllerian hormone (AMH).
- Husband semen analysis
- Transvaginal ultrasound
- Tubal patency test in the form of hysterosalpingography, saline infusion sonosalpingography or Hycosy should ideally be offered prior to ovulation induction.
- For PCOS patients with a BMI more than 25 kg/m^2, lifestyle management for weight loss is recommended. A weight loss of 5–10% of body weight, may even lead to resumption of spontaneous ovulatory cycles in obese anovulatory women with PCOS.

MONITORING OF OVULATION INDUCTION (OI) CYCLES

Ultrasound: Transvaginal ultrasound is always used to visualize the number and size of recruited follicles in stimulated cycles

Table 40.2: Treatment of ovulatory disorders

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
Clomiphene citrate (CC)	It is a selective estrogen receptor modulator (SERM), comprises of 2 stereoisomers zuclomifene and enclomiphene, of which enclomiphene is the more potent isomer. It competetitively blocks hypothalamus and pituitary gland receptors and thus competes with endogenous, and interfering with the negative feedback signalling of natural estrogen. CC binds in the hypothalamus for a longer time compared to natural estrogen, thus prevents the replenishment of estrogen receptors. This causes a hypoestrogenic state in the body which causes GnRH and FSH to be released. CC administration requires an intact HPO axis to have an adequate action. The high levels of FSH cause hyperstimulation of the ovary and the potential for multi-follicular development.[6]	50–150 mg, orally, for 5 days, starting from day 2–5 of menses. The starting dose is 50 mg and it can be stepped up in the next few cycles until the patient ovulates. Maximum dose—250 mg/day.[7] CC Resistance is when patients fail to respond to CC at doses of 250 mg/day or do not ovulate after six cycles . They require re-evaluation and alternate treatments for ovulation induction.	When patient selection is appropriate, CC achieves ovulation in 70–80% women.[6] Live birth rates are between 15% and 20%. CC when combined with IUI, for unexplained infertility is very effective, in an effort to increase the numbers of both ova and sperm.[8]	Mild symptoms, like transient hot flashes (10–20%), headache, pelvic pressure or pain, breast tenderness, and nausea (2–5%)	Multiple pregnancy—7–10%[9] OHSS 0.5–2.5% but these are mild-to -moderate OHSS. Risk of severe OHSS is remote.

(*Contd...*)

Table 40.2: Treatment of ovulatory disorders *(Contd...)*

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
Letrozole	Competitive aromatase inhibitor. Aromatase catalyzes the rate-limiting step of conversion of testosterone to estrogen. Letrozole blocks estrogen production in the periphery and brain, and leads to a compensatory increase in pituitary gonadotropin secretion which causes ovarian follicular development. Similar to clomiphene, letrozole does not work in women a abonormal HPO axis, and those with hypogonadotropic hypogonadism.[10]	2.5 mg /day for 5 days starting from day 2–5 of menses. Maximum dose—7.5 mg/day Extended letrozole protocol—2.5–5 mg/day for 10 days from day 2–5 of menses.	Letrozole is the drug of choice for ovulation induction in anovulatory women with PCOS due to higher live birth rates compared to CC. It is also efficacious for ovulation induction in anovulatory CC resistant women.[10]	Common minor side effects include headaches, cramps, fatigue (20%) and dizziness (12%).[11]	Risk of multiple pregnancy—3–7%.[12] Risk of severe OHSS—negligible.
Metformin	Metformin is an oral insulin-sensitizing biguanide, that acts by reducing hepatic gluconeogenesis and secondarily decreases intestinal glucose absorption and increases its uptake in the periphery.	Initial: 500 mg/day Increase 500 mg/day every week Max. dose 2500 mg day.[14]	A 2017 meta-analysis evaluated the benefit and safety of metformin in improving fertility outcomes for women with PCOS undergoing ovulation induction.	Abdominal pain Nausea Vomiting Diarrhoea Rare lactic acidosis	As a sole therapy, it does not increase the risk of OHSS or multiple pregnancy.

(Contd...)

Table 40.2: Treatment of ovulatory disorders *(Contd...)*

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
	This reduces insulin resistance and androgen concentrations, and helps achieve ovulation in some PCOS women.[13]		It concluded that metformin leads to significantly higher ovulation rates, clinical pregnancy, and live birth rates compared to placebo or no treatment. This meta-analysis also concluded that combination of metformin and clomiphene achieves higher ovulation rate (OR = 1.57, CI = 1.28–1.92) and pregnancy rates (OR = 1.59, CI = 1.27–1.99), compared to treatment with clomiphene alone.[15]		
CC + Metformin		Metformin 1500 mg/day for 6–8 weeks. Initiate CC 100 mg daily for 5 days from day 2–5 of menses.	Combined treatment with metformin and clomiphene is useful in women with clomiphene resistant.		
Letrozole + Metformin		Metformin 1500 mg/day for 6–8 weeks. Letrozole as per normal protocol 2.5 mg × 5 d	A recent study concluded that in PCOS with clomiphene-failure, metformin + letrozole together results in higher pregnancy rates and less abortion than metformin-clomiphene.[16]		

(Contd...)

Table 40.2: Treatment of ovulatory disorders *(Contd...)*

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
Gonadotropins	In type-1 WHO classification system, women are ideal candidates for gonadotropin (Gn) therapy as they do not have an intact HPO axis. These patients require exogenous Gn to overcome the HPO axis inability to produce FSH, to directly stimulate follicular growth and ovulation.[17] Gn treatment is also second-line treatment for anovulatory or PCOS women who have failed first-line oral ovulogens, as the FSH had not reached threshold level required to generate a dominant follicle with oral agents.[18]	Regimens: Recombinant FSH or hMG 1. 'Step-up' treatment regimen in both women with hypogonadotropic hypogonadism (WHO Group I) and those with oral antiestrogen-resistant anovulation (WHO Group II), initially, to induce ovulation , begin with a low daily dose (75 IU, daily) in a 'step-up' treatment regimen. After 4–7 days, a transvaginal ultrasonography, provides the first idea of follicular response. Subsequently, the dose of gonadotropins may be maintained or increased, as seen by the response.	In women with hypogonadotropic hypogonadism, cycle fecundity is approximately 25%, equal to or even greater than that observed in normal fertile women; cumulative pregnancy rates after up to six cycles of gonadotropin stimulation approach 90%.[22] By comparison, cycle fecundity is significantly lower in clomiphene-resistant anovulatory women. Overall, cycle fecundity ranges between 5% and 15%, and cumulative conception rates range between 30% and 60%; within the group, those with hyperandrogenic chronic anovulation have the poorest prognosis.[19]		The multiple pregnancy rate is approximately 15%. The overall incidence of spontaneous miscarriage in gonadotropin-induced conception cycles is approximately 20–25%, moderately higher than generally observed (15%). [23] Risk factors for OHSS include young age, low body weight, high ovarian reserve as indicated by high serum AMH levels or antral follicle count, PCOS, higher doses of gonadotropins, and previous history of hyperstimulation. Risk increases with serum estradiol levels and the number of developing ovarian follicles and when supplemental doses of hCG are administered after ovulation for luteal phase support.[24]

(Contd...)

Table 40.2: Treatment of ovulatory disorders *(Contd...)*

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
		2. 'Low-slow' treatment regimen—low doses (37.5–75 IU daily), small increments, and a longer duration of stimulation are given for ovulation induction[20] 3. 'Step-down' treatment regimen is designed to more closely approximate the pattern of serum FSH concentrations observed in spontaneous ovulatory cycles. The cycle begins with a higher dose (150–225 IU daily) and thereafter decreases gradually in an effort to allow continued development of only the dominant follicle and withdrawing support from the less sensitive smaller follicles in the cohort.[21]			

(Contd...)

Table 40.2: Treatment of ovulatory disorders *(Contd...)*

Drug	*Mechanism of action*	*Dosage*	*Results*	*Side effects*	*Risks*
		4. Sequential regimen: Sequential treatment with clomiphene and gonadotropins can help some clomiphene-resistant anovulatory women. The cycle involves the usual course of clomiphene treatment (50–100 mg daily), followed by low-dose FSH or hMG (75 IU daily) beginning on the last day of clomiphene therapy or the next day; treatment is followed up and monitored subsequently just as gonadotropin-stimulated cycles. The advantage of this treatment was decreasing significantly, (50% or more), the dose and duration of gonadotropin therapy and the associated costs of monitoring.			

and especially in gonadotropin cycles. The endometrial thickness can also be measured. Typically, when the mean diameter of the dominant follicle reaches 18–20 mm, human chorionic gonadotropin (hCG) is given to trigger ovum release; ovulation can be expected to occur around 36–48 hours later and this helps to decide the correct timing of intrauterine inseminisation (IUI) or timed intercourse.

Serum estradiol: In a natural ovulatory cycle, there is a peak in serum estradiol levels between 200 and 400 pg/ml just before the LH surge. Serum estradiol (E_2) levels are expected to rise in a similar way in medically stimulated cycles, for each mature follicle observed. Usually, serum E_2 levels are not routinely used for monitoring. With the current gonadotropin stimulation regimens, it has been observed that positive results are obtained when estradiol concentrations peak between 500 and 1,500 pg/ml; and it has also been seen that pregnancies are not common at levels below 200 pg/m.[4]

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Chapter

41

Drugs to Treat Endometrial Hyperplasia

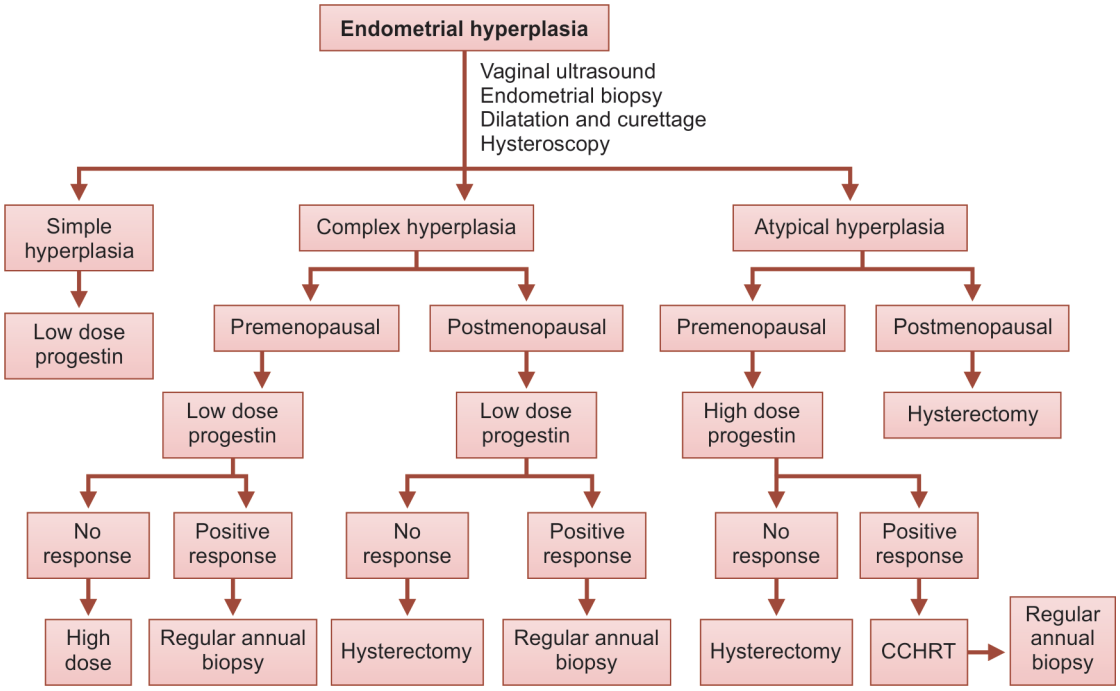
• Kinjal Shah • Sangeeta Agrawal

Introduction

Estrogen helps the epithelial cell proliferation which results in thickening of the uterus, while progesterone helps the epithelial cell differentiation in the secretory phase of the endometrial cycle. The fine equilibrium between endometrial proliferation and apoptosis is maintained by a number of factors like hormonal balance, molecular mechanisms, environment, age, and is prone to various disturbances leading to different endometrial abnormalities **(Flowchart 41.1)**.

Endometrial hyperplasia (EH) is a pre-cancerous, non-physiological, non-invasive

Flowchart 41.1: The investigation and management of endometrial hyperplasia



CCHRT: Continuous combined hormone replacement therapy

proliferation of the endometrium that results in increased volume of endometrial tissue with alterations of glandular architecture (size and shape) and endometrial gland to stroma ratio of greater than 1:1. The majority of cases of EH are due to chronic exposure to estrogen, unopposed by progesterone, such as in earlier forms of hormone replacement therapy. The most common symptom of EH is abnormal uterine bleeding which includes menorrhagia, intermenstrual bleeding, postmenopausal bleeding, and irregular bleeding when on hormone replacement therapy or tamoxifen. Currently, the treatment approaches for EH are limited, such as hysterectomy or hormone therapy. EH without atypia is generally treated with progestins while EH with atypia are advised hysterectomy.

PROGESTIN THERAPY

Progestins are synthetic progestogens with similar effects as progesterone. Progestins are ideally used to induce EH regression in women with EH without atypia or those who wish to retain fertility. Progestins can provide hormonal contraception either alone or with estrogen, and prevent EH development associated with unopposed estrogen. Progestins decrease the glandular cellularity by inducing apoptosis and to inhibit angiogenesis in the myometrium immediately underlying the complex EH. The different routes available to administer progestins are oral, intramuscular, micronized vaginal cream, or intrauterine devices. This treatment has been highly successful in reversing EH with or without atypia in patients on estrogen-alone replacement therapy, and was found to reduce EH in 61% of patients with atypical hyperplasia.

The mode and duration of progestin treatment is assessed on its success to reduce EH. EH usually shows a response after 10-week of dosing, but significant responses are commonly observed after 3-months of progestin therapy, with the median time to resolution being 6 months. Progestin therapy may be continued further or hysterectomy is been advised in cases of no response **(Table 41.1)**.

MEDROXYPROGESTERONE ACETATE

Medroxyprogesterone acetate (MPA) is a synthetic steroidal progestin (synthetic steroid hormone progesterone), used to treat patients with absent or irregular menstrual periods, or with abnormal uterine bleeding. MPA is used to prevent thickening of the endometrial lining in postmenopausal women receiving estrogen hormone therapy and decreases the risk of endometrial carcinoma. MPA is commonly administered at 10 mg per day, orally and continuously for 6 weeks, or cyclically for 3 months (2 weeks of each month). Cyclic MPA is safer and more acceptable therapy than continuous MPA.

MEGESTROL ACETATE

Megestrol acetate (MA) is a steroidal progestin (specifically, 17-hydroxylated progesterone)

Table 41.1: Common dose of various progestins for treatment of endometrial hyperplasia

Progestin type	*Commonly available as*	*Benign/simple hyperplasia*	*Atypical hyperplasia or EIN*
Progesterone	Progestasert, crinone, endometrin	300 mg, PO × 14 day/mo	300 mg/day, PO
Medroxyprogesterone acetate	Depo-provera (injection), provera (oral)	10 mg, PO × 14 day/mo	100 mg PO, or 1000 mg/wk, IM
Megestrol acetate	Megace	80 mg, PO × 14 day/mo	160 mg/day, PO
Levonorgestrel IUD	Mirena, orplant	20 µg/day × 6 mo to 2 yrs	

EIN: Endometrial intraepithelial neoplasia; IUD: Intrauterine device

with predominantly progestational and antigonadotropic effects. It has been shown to have the potential to inhibit proliferation in the uterus and treat EH. MA at doses ranging from 160 to 320 mg/day has been reported to be an effective method of treatment for endometrial pathologies without causing harmful effects on serum lipid profiles or glucose levels.

LEVONORGESTREL

Levonorgestrel (LNG) is a second-generation progestin (synthetic progestogen) commonly used as hormonal contraceptives. The LNG-impregnated intrauterine device (LNG-IUD) is commonly used in the management of endometrial hyperplasia. It contains 52 mg of levonorgestrel and release at a rate of approximately 20 μg/day over a period of 5 years. Common side effects associated with levonorgestrel are headache, acne, breast tenderness, irregular bleeding, mood changes, cramping or pelvic pain.

NORETHINDRONE ACETATE OR NORETHISTERONE ACETATE

Norethisterone (or norethindrone) is a synthetic, orally active steroidal progestin with antiandrogen and antiestrogen effects. Various studies have been performed on the use of norethisterone to reduce the incidence of EH in postmenopausal women treated with estradiol and has been found to be very effective. There are some common side effects like dizziness, headache, nausea, abdominal pain, uterine pain, delay of menstruation, heavy menstruation, uterine bleeding, fatigue, diarrhea, vomiting, and painful menstruation associated with norethisterone.

Failure of progestin treatment depends on multiple factors such as patient's age, health, other diseases, and hyperplasia grade or type. Hence, precautions, such as routine checkups and biopsies are recommended for patients while on progestin therapy.

THERAPIES OTHER THAN PROGESTINS

1. Danazol

Danazol is a synthetic androgen, which is a derivative of 17α-ethinyl testosterone which is commonly used in the management of endometriosis. Danazol can induce a hypoestrogenic, as well as, a hypoandrogenic state in the uterus, resulting in atrophy of the endometrium. Danazol is an effective and safe alternative to progesterone for management of EH. However, some studies have shown that danazol can increase the risk of ovarian cancer in women with endometriosis. Other side effects associated with danazol include weight gain, muscle cramps, acne, seborrhea, decreased breast size, hirsutism, and deepening of the voice, which are all strongly related to androgenic action.

2. Genistein

Genistein is an isoflavonoid extracted from soy products which acts as an inhibitor of protein-tyrosine kinases and topoisomerase-II. Genistein suppresses estrogen-induced genes, such as c-fos and c-jun, as well as the internal cytokines interleukin-1α (IL-1α) and tumor necrosis factor-α (TNF-α) through cytokine- and ER-mediated pathways. Treatment with genistein aglycone (54 mg/day, n = 19) for 6 months has shown a 42% positive response rate in premenopausal women with non-atypical EH.

3. Metformin

Metformin (N,N-dimethylbiguanide) belonging to a class biguanides is commonly used for the treatment of type-2 diabetes mellitus and polycystic ovary syndrome (PCOS), especially in over-weight and obese individuals, or in cases when insulin resistance may be an important factor. Since insulin resistance is associated with the occurrence of atypical EH and metformin was shown to have anti-proliferative, anti-invasive, and anti-metastatic effects in multiple cancers, use of metformin is a logical approach for the

treatment of EH. Metformin was shown to induce progesterone receptor (PR) expression in endometrial cancer cells, which may enhance progestin therapy efficiency or overcome the progestin resistance caused by PR depletion in long-term progestin therapy.

4. Gonadotropin-releasing Hormone Therapy

The endometrium contains gonadotropin-releasing hormone (GnRH) receptors and GnRH agonists which downregulate GnRH receptors upon prolonged exposure. GnRH analogues suppress the hypothalamic pituitary–ovarian (HPO) axis, thereby resulting in inhibition of estrogen production. Thus, GnRH analogues have a direct anti-proliferative action on endometrial cells. The ideal dose administered of GnRH is 1 ampule/3.75 mg, intramuscularly, every 28 days for 6 months to treat women with EH, with or without atypia. Further studies are needed to determine the usefulness of GnRH analogues in patients with atypical endometrial hyperplasia.

5. Aromatase Inhibitors

Aromatase inhibitors can inhibit estrogen production and thus reduce estrogen levels. Examples of aromatase inhibitors include letrozole (Femara; Novartis, Basel, Switzerland), anastrozole [Arimidex, AstraZeneca, London, United Kingdom (UK)], and exemestane [Aromasin, Pfizer, New York, NY, United States of America (USA)], which are commonly used to treat breast cancer, and also thought to be helpful in the treatment of endometrial cancer. Anastrozole or letrozole were shown to reduce endometrial thickness in patients with EH. Recent studies have established letrozole as good therapeutic option for simple EH without atypia.

Anastrozole was also found to be a new modality for the management of EH in obese postmenopausal women. Side effects of aromatase inhibitor may include joint and muscle pain as well as hot flashes, bones weakening and occasionally osteoporosis.

SURGICAL MODALITIES

Since EH can progress to endometrial carcinoma, surgery is advised in most women with complex EH with atypia if the childbearing is completed and do not desire preservation of their fertility or did not respond to hormone therapy. Several surgical options have been widely reported as common treatments of atypical EH, such as thermal balloon ablation, laser therapy or resectoscopic surgery. Hysterectomy might be considered a first-choice treatment for EH. Resectoscopic surgery is an effective treatment for EH without atypia, especially for those at high risk for medical therapy or hysterectomy. It is also recommended that postmenopausal women with atypical EH undergo hysterectomy with bilateral salpingo-oophorectomy rather than hysterectomy alone.

Currently, the recommended treatment approach for EH includes the following, cyclic progestin therapy, GnRH therapy, and hysterectomy. Progestins continue to be an effective option, especially for patients with low-grade estrogen receptor (ER) and/or PR/positive disease, some of whom achieve prolonged remission. The disadvantages of GnRH therapy include high cost, menopausal symptoms and bone demineralization associated with prolonged therapy. Fat tissues are the most common site for conversion of androgen to estrogen.

CONCLUSIONS

Endometrial hyperplasia being a precursor of endometrial cancer is of clinical importance. Available therapeutic options for EH, are progestin, danazol, genistein, metformin and GnRH therapy or surgery which is indicated in women with restricted efficacy due to high cost, side effects and drug resistance. Endometrial hyperplasia still remains a challenge in patients who wish to retain their fertility. As a novel approach, the antiestrogens, aromatase inhibitors and

cytokines might give optimistic outcome for EH; however, clinical trials are needed to prove their efficacy. Future investigations and clinical trials with these novel compounds in combination with known established EH therapies are required to achieve precise management of EH. Further research on the cellular signaling pathways that control endometrial cell proliferation and development of EH, as well as targeting various mutations and single nuleotide polymorphisms (SNP) in pathobiology of EH will help to identify novel targeted therapeutic agents to improve the management of EH.

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Chapter

42

Drugs to Treat Thin Endometrium

• Devika Chopra • Priya Vora • Manan Boob

Introduction

The uterine endometrium serves as the receptive ground for the implantation of an embryo during the mid-luteal phase of the menstrual cycle. It undergoes intricate changes in response to estrogen and progesterone, preparing it for implantation. These changes occur at the morphological, biochemical, and molecular levels, and any disturbance at these levels can lead to unsuccessful implantation.[1]

Various ultrasound markers, including endometrial thickness (EMT), endometrial blood flow, and uterine volume, have been studied to detect a receptive endometrium. However, their specificity and positive predictive value have been found to be low. A triple-line endometrium observed on ultrasonography on the day of the human chorionic gonadotropin (hCG) trigger, has been linked to successful implantation. Although a minimum endometrial thickness of 6 mm has been considered important for achieving implantation in assisted reproductive technologies (ART), there have been documented cases of successful pregnancies with a minimum EMT of 4 mm.[2] Many ART centres have their cut-off value for EMT ranging from 7–10 mm, below which the success of the ART cycle is reduced.

Numerous mechanisms have been suggested to elucidate the underlying pathophysiology of thin endometrium. These include intrauterine adhesions, ovarian stimulation using clomiphene citrate (CC), and prolonged use of progesterone and combined oral contraceptive pills (COCPs).[3] As a result, several treatment options have been proposed to enhance endometrial thickness and subsequent endometrial receptivity for patients with this condition.

HOW TO MEASURE ENDOMETRIAL THICKNESS

To minimize inter-operator variation, it is crucial to adopt a consistent method for measuring EMT. The recommended approach involves using a transvaginal probe with an empty bladder, as this brings the probe closer to the endometrium, resulting in higher-frequency waves compared to the transabdominal probe.[4] When measuring EMT, it is best to do so in the sagittal plane or long axis. The measurement should be taken from the thickest echogenic area, starting from one stratum basalis endometrial interface across the endometrial canal to the other stratum basalis interface **(Fig. 42.1)**. The surrounding inner myometrial lucency should not be included in this measurement. This standardized method ensures more accurate and consistent EMT assessments across different operators.[4] This measurement is usually found within 1 cm of the fundal tip.[5]

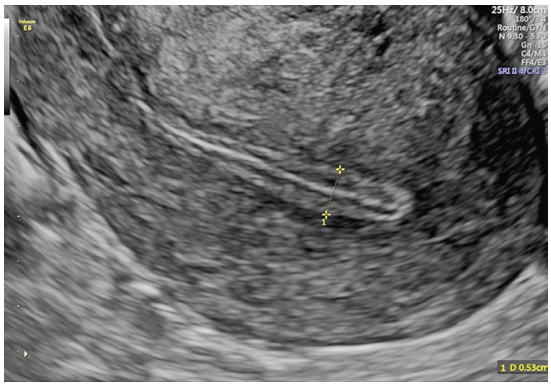

Fig. 42.1: Measurement of endometrial thickness[5]

TREATMENT OF THIN ENDOMETRIUM

A thin endometrium is a complex condition influenced by various factors, and its management should be targeted at addressing the underlying causes. The primary objective of treatment is to enhance endometrial receptivity and facilitate successful implantation. Nonetheless, managing patients with thin endometrium poses considerable challenges, leading to the exploration of multiple treatment regimens in the existing scientific literature **(Fig. 42.2)**.[6]

Aspirin

According to the hypothesis, the administration of low-dose aspirin (at 75 mg) is believed to enhance endometrial blood flow by reducing uterine artery impedance. Studies have shown that low-dose aspirin can lead to a decrease in the pulsatility index of the uterine artery, ultimately contributing to an improvement in pregnancy rates.[7]

A single, non-blinded randomized controlled trial (RCT) has investigated the application of low-dose aspirin in patients with thin endometrium. This study enrolled 28 recipients of donor oocytes who had previously experienced an endometrial thickness of less than 8 mm in a prior cycle. The participants were randomly assigned to receive either aspirin treatment or no intervention. The results of the study indicated that there were no significant differences observed between the two groups regarding EMT, pregnancy rate, or live birth rates.[8] Based on a Cochrane study, low-dose aspirin has no substantial positive effect on pregnancy and endometrial thickness.[9]

Luteal Estradiol

The endometrium is a hormone-dependent tissue, and its growth and development are regulated by estrogen. Estrogen plays a crucial role in supporting the proliferation of the endometrial tissue. It achieves this by causing contraction of the spiral arteries and reducing the oxygen tension in the functional layer of the endometrium. These changes create a favorable environment for embryo implantation to occur successfully.[10]

Both oral estrogen in the form of micronized estradiol and estradiol valerate have similar effectiveness. Estrogen can also be administered vaginally, and this route is associated with the highest levels of serum and endometrial estradiol. In cases where oral administration proves ineffective, the vaginal route is preferred.

A study compared the effects of oral and vaginal administration of estradiol in donor–egg recipients. The results indicated that women who did not achieve an acceptable endometrial thickness after oral estradiol administration experienced an increase in endometrial thickness and an improved ongoing pregnancy rate when switched to vaginal estradiol administration for 4–6 weeks. This suggests that the vaginal route can be more effective in certain cases, where the oral route was not successful in achieving the desired EMT.[11]

Research has demonstrated that the prolonged administration of estradiol valerate during controlled ovarian hyperstimulation (COH) cycles leads to notable improvements in mean endometrial thickness. The endometrial thickness increased from an average of 6.7 mm to 8.6 mm. Pregnancy rates increased to 38.5% in the extended administration group, while they were only 4.3% in the group

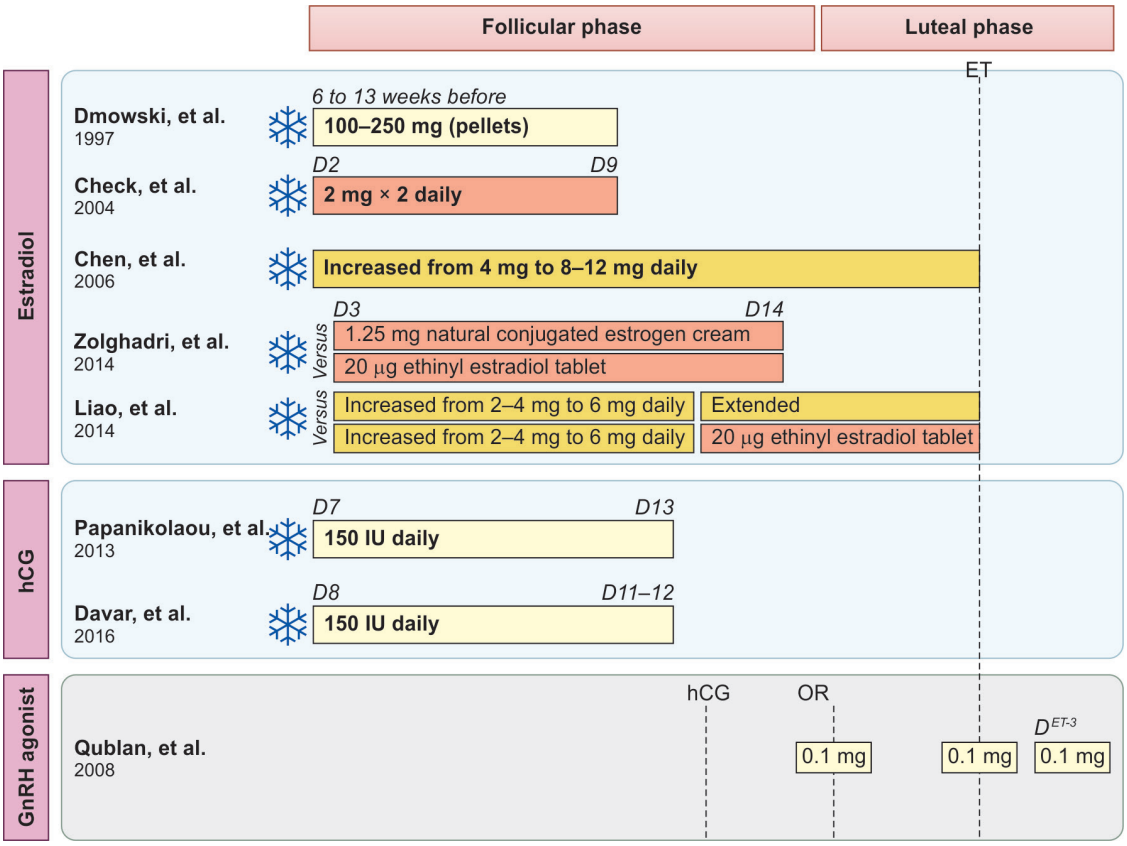

Fig. 42.2: Vascular therapeutic options for thin endometrium before an embryo transfer. Blue background with frozen flake identifies the frozen embryo transfer (FET) cycle. Timing for treatment introduction and ending are specified (D, day; S, stimulation day; *i.e.* D1, first day of the menstrual cycle). The administration route is represented: Vaginal in red, oral in dark yellow, and electrostimulation in orange. ET: Embryo transfer; hCG: Human chorionic gonadotropin; GnRH: Gonadotropin-releasing hormone

with conventional administration. These findings suggest that the extended use of estradiol valerate can have a positive impact on endometrial thickness and significantly improve the likelihood of achieving successful pregnancies during COH cycles.[12]

hCG Priming in the Follicular Phase

Human chorionic gonadotropin plays a crucial local paracrine role in the regulation of endometrial differentiation and receptivity. It exerts its effects by stimulating the release of various cytokines and growth factors within the endometrium. This complex signaling process contributes to the enhancement of endometrial receptivity, making it more favorable for embryo implantation.[13]

In a pilot study conducted by Papanikolaou et al., a group of 17 patients with a resistant thin endometrium (measuring <7 mm) was enrolled during fresh or frozen donor-embryo cycles. To address the thin endometrium, the patients received daily doses of 150 IUs of hCG for 7 days, beginning on either day 8 or day 9 of estrogen administration. The study revealed that the mean EMT increased significantly from an average of 5.18 mm to 6.01 mm (P = 0.008) following the hCG treatment. However, it is worth noting that approximately 29.4% of the patients (5 out of

17), did not experience any improvement in EMT despite the intervention.

After the treatment, the overall pregnancy rate among the patients was 52.9%, with 9 out of 17 patients achieving successful pregnancies.[14]

GnRH Agonist in Luteal Phase

Gonadotropin-releasing hormone agonists are synthetic peptides designed to mimic the structure of natural GnRH, which is released in a pulsatile manner by the hypothalamus. When given in a chronic manner, these agonists suppress normal pituitary–gonadal function and lead to downregulation of the pituitary axis. The potential benefits of GnRH agonists on embryonic development have led to the investigation of their impact when administered as a single dose during the luteal phase in oocyte recipients. This study aimed to explore whether a single administration of GnRH agonist at the time of implantation could enhance the developmental potential of the embryos in these recipients.[15] In this study, GnRH administration improved both the implantation rate as well as the live birth rate.[15] In a study involving 120 women with thin endometrium who were undergoing in vitro fertilization (IVF), two groups were formed. The case group received triptorelin (0.1 mg) on the day of ovum pickup, on the day of embryo transfer, and for 3 days afterward. The control group was given a placebo. The results showed that the treatment with GnRH agonist (GnRHa) led to a significant increase in EMT, implantation rate, and pregnancy rate compared to the control group. This suggests that the use of GnRHa can be beneficial in improving the outcomes of IVF in patients with thin endometrium.[16]

Sildenafil

Sildenafil citrate is an inhibitor of the (cGMP) specific phosphodiesterase type-5 (PDE5) enzyme. By inhibiting PDE5, it prevents the breakdown of cGMP, leading to increased effects of nitric oxide on vascular smooth muscles. Studies have shown that sildenafil citrate administration can also increase uterine blood flow. This effect is achieved through increased p53 activity and elevated levels of endometrial vascular endothelial growth factor (VEGF).

When combined with estrogen, sildenafil citrate may facilitate the estrogen-induced proliferation of the endometrial lining. This combination treatment could potentially improve endometrial receptivity and support successful embryo implantation in certain cases, especially for patients with thin endometrium or inadequate blood flow to the uterus.[17]

An RCT reported enhanced EMT with triple-line endometrial pattern in 77.5% of patients in the sildenafil group *versus* 30% in the control group ($p < 0.001$). In addition, the chemical pregnancy rate was higher in the sildenafil group.[18]

GRANULOCYTE COLONY-STIMULATING FACTOR

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein with various roles, including promoting hematopoiesis and aiding in endometrial growth. In 2011, Gleicher, et al. first reported the successful use of G-CSF intrauterine infusion. They found that patients who had previously been resistant to conventional treatments experienced EMT expansion to at least 7 mm within 48 hours after the G-CSF intrauterine infusion. This indicates that G-CSF treatment can be effective in improving endometrial growth in cases, where standard therapies were not successful.[19]

Barad, et al. (2014)[24] conducted a double-blinded study, randomizing patients to receive either G-CSF intrauterine infusion or a placebo. The study found that there were no significant differences in clinical pregnancy rate and mean endometrial thickness between the G-CSF group and the control group.

Similarly, Xu, et al. prospectively randomized 30 patients with EMT <7 mm during frozen-

thawed embryo transfer cycles to receive either intrauterine G-CSF or G-CSF with endometrial scratch, while 52 patients served as the control group. The study showed a significant increase in EMT after treatment (D 3.9 ± 2.0 mm, P <0.001) with no difference between the two subgroups (G-CSF *vs*. G-CSF + scratch). Moreover, both treatment subgroups had significantly higher implantation and clinical pregnancy rates compared to the control group (31.5% *vs*. 13.9%, P <0.01, and 48.1% *vs*. 25.0%, P = 0.038, respectively).[20]

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) prepared from fresh whole blood containing growth factors and cytokines, has gained popularity in various clinical settings. However, its application to improve EMT has not been extensively studied.

Chang, et al. introduced intrauterine infusion of PRP as a novel approach for treating thin endometrium. They prepared PRP from autologous blood through centrifugation and administered 0.5–1 ml of PRP on the tenth day of the ART cycle. If EMT did not improve 72 hours later, additional PRP infusions were given in each cycle. Embryo transfer was carried out, once the endometrial thickness reached more than 7 mm. The study reported successful endometrial growth and pregnancies in all patients after PRP infusion.[21]

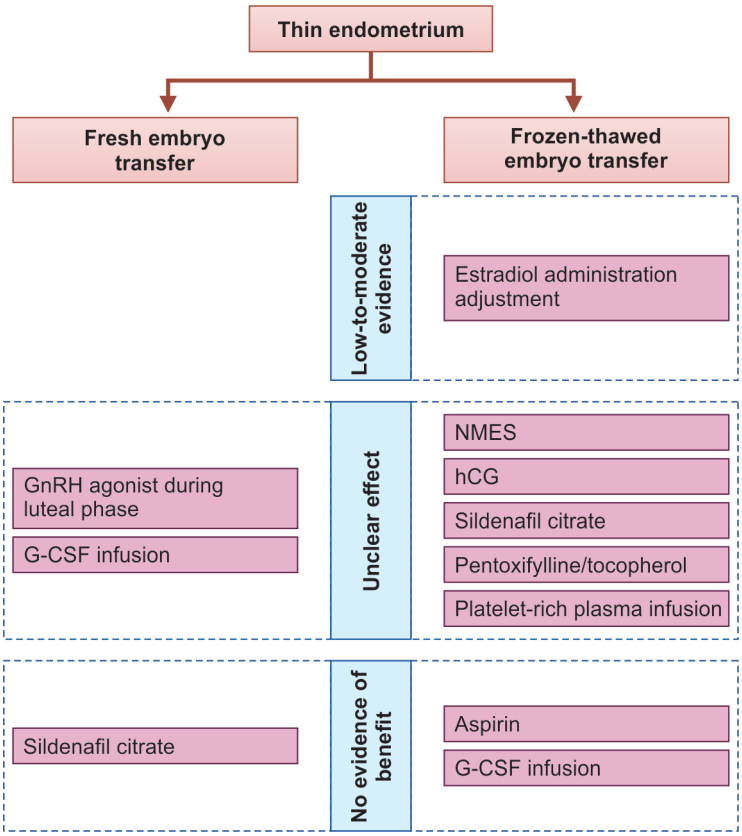

Fig. 42.3: Summary of proposed strategies in case of thin endometrium. The left side shows interventions in fresh cycles and the right side shows interventions in frozen cycles. In dark purple, treatments with low-to-moderate evidence. In light purple with a dotted border, strategies with unclear effects. In pale purple without border, interventions with no evidence of benefit.[23] NMES: Neuromuscular electrical stimulation

In another study, 10 patients undergoing frozen embryo transfer (FET) received intrauterine infusion of PRP. The results showed that the endometrial thickness increased following the PRP infusion, and 50% of the patients achieved pregnancy. These findings suggest that PRP may have a positive impact on endometrial growth and can potentially improve the chances of successful pregnancy in patients undergoing FET.[22]

CONCLUSION

In conclusion, the endometrium's receptivity is vital for successful embryo implantation, and proper endometrial growth is crucial in this process. While poor endometrial development is linked to reduced pregnancy chances, it is not the sole predictor, and the endometrial pattern may be more significant. Vaginal sildenafil during the stimulation cycle seems like a reasonable first-line treatment option, and intrauterine G-CSF infusion before ovulation trigger could be considered as a second-line option. However, larger randomized studies evaluating outcomes and optimal timing and dosage for G-CSF administration are needed to further assess its efficacy.

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Chapter 43

Ormeloxifene in Mastalgia and Benign Breast Disorders

• Reshma Jaydeep Palep

Introduction

Ormeloxifene has shown a very good role in the regression of fibroadenomas instead of the most commonly used medicine evening primrose oil (EPO) or surgical removal of lumps, especially in young girls where cosmesis and damage to lactiferous glands which is a big concern. It is a safe non-steroidal drug to treat mastalgia, particularly in comparison to other medicines used at the moment.

MECHANISM OF ACTION

Ormeloxifene (centchroman—$C_{30}H_{35}NO_3$), is a unique drug first discovered and developed by our own Central Drug Research Institute, Lucknow, India.[1] It is a non-hormonal, non-steroidal oral contraceptive pill.[2] It is a selective estrogen receptor modulator (SERM), the mechanism of action is through the estrogen receptor[3,4] with a weak agonist action on the endometrium and a strong antagonist action on the breast ductolobular epithelium.[5] Hence, it acts on breast lumps, via the estrogen receptor to cause a regression in the size.[2] It is not Food and Drug Administration (FDA) approved, used only in India, presently.

PHARMACOKINETICS

Oral intake is the only route of administration for this drug. Absorption of the drug after a 60 mg oral dose showed a maximum serum concentration (C_{max}) varying from 117 to 129 ng/ml after 4 hours of the drug being ingested.[6] In patients who were given 30 mg tablets, it was shown that C_{max} was 30.45 to 78.41 ng/ml after 3 to 8 hours.

DOSAGE

Patients are given ormeloxifene 30 mg on alternate days for 3 months for fibroadenomas and are called for check-up at 3 months and 6 months.[7]

For mastalgia, the patients are given oral ormeloxifene 30 mg twice a week for 3 months.[8]

SIDE EFFECTS

Common side effects are nausea, headache, rise in blood pressure, weight gain and delayed or prolonged menstrual period.

In most of the studies for ormeloxifene given for breast lesions, major side effects requiring the patient to withdraw from the study were not seen. The common side effect was menstrual abnormality, in which the patients reported missing their menstrual periods. In some patients, the duration of cycle was also extended, but these normalised after stopping the medication within 12 weeks and hence were not a huge concern.[9]

Ormeloxifene does affect the endocrine, hepatic systems or lipid function. It does not pose any serious complications like thrombosis heart attack or stroke.[6,10]

It does not affect ovulation, and so there is no effect on fertility which can be a major concern of the patients in the reproductive age group.[11] However it acts as a contraceptive due to its effect on the endometrium which is reversible.[4]

CLINICAL APPROACH

Mastalgia

The role of ormeloxifene in regression of mastalgia with or without fibroadenomas has also been scrutinised in various studies so far. Several medicines have been tried for mastalgia and benign breast disorders. There are two categories of medicines which can be used for these problems and can be classified into hormonal and non-hormonal. Hormonal formulations which have been used are danazol, tamoxifen, bromocriptine, progesterone, oral contraceptive pills, luteinizing hormone-releasing hormone (LHRH) analogue or goserelin. The non-hormonal formulations include analgesics, EPO and gamma linolenic acid (GLA).

In a study conducted at the All India Institute of Medical Sciences, New Delhi, India it was found that after 3 months of treatment with ormeloxifene, 90% patients were free of pain.[11] Results like these have made the usage of this drug a big boon to young girls, seeking relief from pain.

The drug was found to be more efficacious with faster response in patients who had a cyclic pattern of mastalgia. Total relief of pain was found in 66% of cyclic mastalgia and 40% of non-cyclic mastalgia patients after 1 week of treatment.[12]

Another study which compared the effectiveness of ormeloxifene and tamoxifen in bringing about pain relief in patients of mastalgia, found the results to be similar in both groups. However, a higher incidence of side effects, especially ovarian cyst formation in the patients who were put on ormeloxifene was a bit worrisome.[13]

In comparison to danazol in the treatment of mastalgia, ormeloxifene scores over danazol in ameliorating the pain score, reduction was seen after 24 weeks of treatment ($p = 0.019$) and was hence considered a better, safer and less expensive solution to danazol devoid of major side effects in order to treat patients with mastalgia.[14]

Fibroadenomas

In a randomized controlled trial of 48 patients and 48 controls which was conducted, it showed that there is regression of fibroadenoma in 60% of women receiving ormeloxifene and 30% in the control arm.[11]

Ultrasound breast was used to measure fibroadenoma volume and also estrogen-receptor studies were done which showed that the receptor positivity was 40%. It was also observed that patients who are receptor-negative status also responded to ormeloxifene. The reason for the response of the receptor-negative lesions is difficult to ascertain. It is presumed that the drug may be acting through some unknown pathway.[11]

Mastalgia and Fibroadenomas

Ormeloxifene is a good drug to bring about an effective reduction in pain (mastalgia) as well regression in the size of the of fibroadenomas. A study that has looked at both parameters has found that the visual analogue scores (VASs) in mastalgia patients were decreased to ≤3. They also have noted a complete response in 34%, partial dissolution in 46% and no response in 17%.[7]

A large prospective study of 100 women in the reproductive age group (up to 35 years) found that ormeloxifene is a unique non-steroidal drug and considered to be the pride molecule for India. It has been found to be effective in reducing the symptoms of mastalgia as well as helping in reducing the size of fibroadenoma within 3 months.

97.6 to 100% of women in mastalgia group were found to have complete relief of pain which is a tremendous response and 28% of fibroadenoma patients reported complete regression after 3 months of treatment.[15]

Another prospective clinical study of 142 patients over 6 months in all, comprised of patients who came with the complaints of breast symptoms of a lump or pain who were below 30 years of age. At the end of 3 months, 19 (43.1%) patients had a decrease in lump size in the ormeloxifene group whereas in 4 patients (12.5%), a decrement was seen in the placebo group. At the end of 6 months, 23 (52.2%) patients had a reduction in the size of the lump whereas in only 7 (21.8%) patients in the placebo arm showed a decrease in size. 14 (31.8%) patients had complete regression of the lump, as compared to only 5 (15.6%) patients on the placebo arm. Due to a similarity in etiology, *i.e.* hyper responsiveness of the breast tissue to estrogen, ormeloxifene is considered to be the best drug in the conservative management of benign breast disorders. They cause a significant reduction in the size of the fibroadenoma, nodularity, to the extent that they may regress completely and also cause amelioration of pain with minimal side effects. It also reduces the risk of surgery and anaesthesia, avoids bad cosmesis due to scar contracture or any damage to the lactiferous glands. There is no hospitalisation required in the treatment.[16]

In conclusion, ormeloxifene is found to be better that the drug therapies presently being used since it is a nonsteroidal molecule and hence does not have the steroidal side effects even if used for long-term therapy. It is easy to administer, as long as patients remember to take it on alternate days for breast problems and shows good patient compliance. The significant relief of symptoms in the young patients who are anxious and distressed due to pain and lumps results in higher satisfaction as well. After 6 months, it was found that the patients who needed surgeries were reduced and there was a good response to the treatment.[7]

The drug has been found to be of great benefit not only in mastalgia, but also in regression of fibroadenomas and fibrocystic conditions as well.[17]

ANTI-CANCER AGENT

The role of ormeloxifene as an anti-cancer agent has been established in breast and uterine cancer[18,19] due to its strong estrogen antagonistic action.[2] Apart from this, similar to many SERMs, ormeloxifene also has an effect on modulation of other signalling pathways which are not dependent on ER expression to regulate the growth of cancer cells. This drug has also been studied for its suppressive role in other cancers, like chronic myeloid leukaemia and head and neck squamous cell carcinoma.[19] The anti-cancer activity of ormeloxifene can be further improved by encapsulation using hyaluronic acid (HA), which improves targeted delivery to a large extent.[20]

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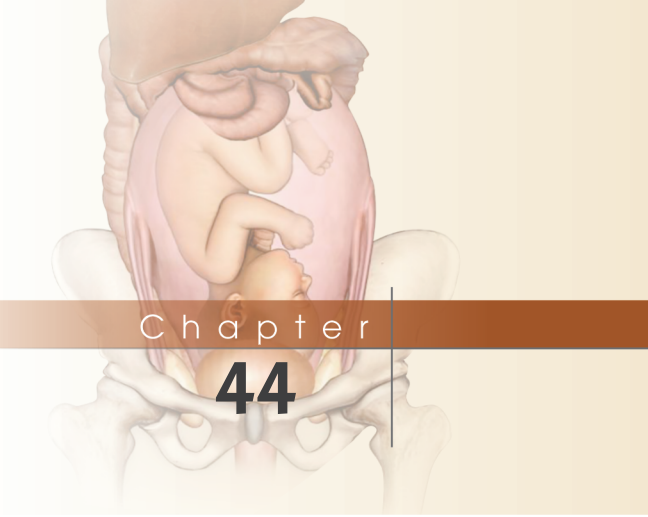


Chapter
44

Pharmacotherapy in Endometriosis

• Mamta Gupta

Introduction

Growth of endometrial tissue outside the uterus is termed endometriosis. The condition is estrogen-dependent and about 10% of females of reproductive age are affected.[1] Endometriosis is diagnosed in 21–47% in women with subfertility and 71–87% of women with chronic pelvic pain.[2] Endometriosis occurs rarely in postmenopausal women.[3] It is considered a benign disorder, yet, endometriosis can affect the patient's quality-of-life. Sampson hypothesized retrograde flow of sloughed endometrial cells into the pelvic cavity from the fallopian tubes and subsequent implantation onto the peritoneum, results in the growth of endometriotic lesions. These lesions have the same steroid receptors as normal endometrium. Microscopic internal bleeding, inflammation, neovascularization, and fibrosis also do occur.[4] These ectopic implants are located in the pelvis, *i.e.* ovaries, fallopian tubes, vagina, cervix, or uterosacral ligaments or rectovaginal septum. More unusual implantation sites are scars, pleura, spleen, gallbladder, spinal canal, stomach, etc.[5,6]

Symptoms

Pelvic pain in the form of dysmenorrhea, deep dyspareunia, non-cyclical chronic pelvic pain, lower abdominal pain and back pain.[7]

Pain usually precedes the onset of menses and lasts for the duration of the cycle. Other symptoms include fatigue, infertility and heavy menstrual bleeding. Non-gynaecological cyclic symptoms can occur, including dyschezia, dysuria, urinary frequency, abdominal bloating, nausea, and vomiting and inguinal pain. One-third women will have no symptoms (asymptomatic).[1]

Diagnosis of endometriosis is predominantly clinical, but the definite diagnosis is usually confirmed by surgery and suspicious lesions biopsied for histology.

There is currently no cure for endometriosis. The goals of endometriosis treatment may include symptom relief and/or enhancement of fertility by medications and/or surgery depending on the following:

- Age
- Current symptoms and their severity
- Severity of the disease
- Desire for children
- Tolerance to various medications, procedures and therapies

Long-term and repeated treatment is required in most of the cases. Also, symptoms of endometriosis may return after the treatment is stopped or, in the case of surgery, as more time passes after the procedure.

Treatment is not required in women with no fertility problems without or with minimal

symptoms. However, during follow-up, if symptoms arise or get worsen appropriate treatment is required.

Rationale of Conventional Pharmacotherapy in Endometriosis

Endometriosis depends on the woman's cyclic production of menstrual cycle hormones and provides the basis for medical therapy. Thus, combined oral contraceptive pills (COCPs), danazol, progestational agents, and gonadotropin-releasing hormone (GnRH) analogues, androgens hormones interrupt the normal cyclic production of reproductive hormones and form the mainstay of treatment. Aromatase inhibitors can be used for refractory or recurrent endometriosis.

Medical treatment of minimal or mild endometriosis has not been shown to increase pregnancy rates[8] and no benefit is derived from ovulation suppression in subfertile women with endometriosis who wish to conceive. Moderate-to-severe endometriosis should be treated surgically.[9]

Medical treatment is indicated for relief of pain, to slow the growth of endometriosis lesions, to stop recurrence of disease.

Various options for medical management of endometriosis include non-steroidal anti inflammatory drugs (NSAIDs), hormones, gonadotropin analogues and aromatase inhibitors. Some newer drugs which are still under trial, might contribute to the management of endometriosis.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs, such as ibuprofen or naproxen sodium to help relieve pelvic pain and menstrual cramping. No effect on endometrial implants or progression of endometriosis has been observed with NSAIDs.

NSAIDs are used as first line of drugs with or without oral contraceptives or progestins.

Pharmacokinetics

NSAIDs are well-absorbed from the gastrointestinal tract, with the exception of aspirin (and possibly diclofenac, tolfenamic acid and fenbufen) which undergoes hydrolysis to form salicylic acid. NSAIDs, if given with food or antacids may lead to delayed or reduced absorption. Immediate-release tablets (such as diclofenac potassium), are more rapidly absorbed compared with extended-release formulations. NSAIDs are highly bound to plasma proteins (mainly albumin), with low levels of distribution in the extracellular spaces. The elimination of these drugs depends largely on hepatic metabolism; renal excretion of unchanged drugs is usually small.

Mechanism of Action

The main mechanism of action of NSAID is the inhibition of the enzyme cyclooxygenase-1 (COX-1) and/or cyclo-oxygenase-2 (COX-2) required to convert arachidonic acid into prostaglandins (PGs).[10] PGs decrease the threshold to noxious stimuli. In soft tissues, prostaglandin E_2 (PGE_2) causes pain and inflammation.

COX-1 is expressed in all tissues and ensures gastric mucosal integrity. COX-2 is not expressed in tissues; but its expression is induced during an inflammatory response. NSAIDs are inhibitors of COX-activity and either selectively inhibit the COX-2 enzymes or nonselectively inhibit both the COX-1 and the COX-2 enzymes, making the nonselective NSAIDs a higher risk for ulcerogenic and other adverse effects.[11] Most commonly used NSAIDs inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (*e.g.* celecoxib) only target COX-2 and provide anti-inflammatory relief without compromising the gastric mucosa.[11]

NSAIDs have a favourable effect in women with primary dysmenorrhea. Although endometriosis is a condition of secondary dysmenorrhea, it seems reasonable to consider NSAIDs as a first-line treatment in women with suspected endometriosis-associated pain.[12]

Dosage (Table 44.1)

Start before the start of menstruation in order to block the endometriosis-associated PG formation that leads to pain and swelling. Because of the variability in interindividual response, if the first NSAID is not effective, another NSAID should be tried. No NSAID has been found to be superior to another. If they are effective in controlling the pain, no other procedure or medical treatment is needed. If not, then NSAID may be combined with a hormonal preparation.

Adverse Effects of NSAIDs

NSAIDs may have different safety profile according to inhibition of COX-1 or 2 or both. COX-1 inhibition may cause gastric ulcer and gastrointestinal (GI) bleeding. COX-1 and 2 inhibition may cause Na and K retention, hypertension and hemodynamic kidney injury. COX-2 > COX-1 inhibition may cause myocardial infarction and stroke because of increased risk due to platelet aggregation and vasoconstriction.

- *Gastric adverse effects* are more likely in a patient that has a prior history of peptic ulcers. Since it is COX-1 specific, COX-2 selective NSAID is an alternative.[15] NSAIDs should be administered with plenty of water and on a full stomach to protect the gastrointestinal tract from the loss of cytoprotective PGE_2. Women having history of gastric irritation, ulceration, and bleeding should avoid COX-1 inhibitors.
- *Renal adverse effects* does not pose a large problem, in a patient with normal renal function. However, in a patient with renal dysfunction or when give on chronic basis, renal injury can occur. This can lead to acute renal dysfunction, fluid and electrolyte disorders.[16] NSAIDs should not be administered on a chronic basis as renal injury can result.
- *Cardiovascular adverse effects* can be increased with NSAID use; these include myocardial infarction (MI), thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.[17]

Table 44.1: Commonly used NSAIDs used and their dosage[13,14]

Drug	*COX-2 selectivity*	*Tablet amount*	*Dose and frequency*	*Upper daily limit*
Ibuprofen	Moderate	200 mg	1 tab, 4–6 hrly	1200 mg
Ketoprofen	Low	50 mg	1 tab, 6 hrly	300 mg
Naproxen	Low	220 mg	1 tab, 8–12 hrly	660 mg
Aspirin (acetyl salicylic acid), low dose	Low	80 mg	4–6 tab, 4–6 hrly	4000 mg
Aspirin, regular strength	Low	325 mg	1–2 tabs, 4 hrly	4000 mg
Aspirin, extra strength	Low	500 mg	1–2 tabs, 6 hrly	4000 mg
Acetaminophen (paracetamol), regular strength	High	325 mg	2 tabs, 4–6 hrly	4000 mg
Acetaminophen, extra strength	High	500 mg	1–2 tab, 6hrly	4000 mg
Acetaminophen, extended release	High	650 mg	1–2 tabs, 8hrly	4000 mg
Diclofenac	High	50 mg	1 tab, 8 hrly	200 mg
Diclofenac	High	100 mg	1 tab, 12 hrly	200 mg
Celexocib	High	200 mg	1 tab, daily	400 mg

- *Hepatic adverse effects* are less common; Among the various NSAIDs, diclofenac has a higher rate of hepatotoxic effects.[18]
- *Hematologic adverse effects* can occur, particularly with nonselective NSAIDs due to their antiplatelet activity. This effect poses a problem if the patient has history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.), and in some perioperative cases.[19]
- *Other minor adverse effects* include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.[20,21] NSAIDs may inhibit ovulation which is reversible after stopping its use. This may be of concern in a woman wanting to conceive. The inhibition is more with diclofenac and less for naproxen.[22]

Contraindications

NSAID hypersensitivity or salicylate hypersensitivity, peptic ulcer/GI bleed, kidney disease, inflammatory bowel disease, congestive heart failure, brain stroke (except aspirin), myocardial infarction (except aspirin), coronary artery disease, who have undergone gastric by-pass surgery or coronary artery by-pass graft surgery.

Drug interactions: NSAIDs decrease efficacy of diuretics, and inhibit elimination of lithium and methotrexate, increases risk of bleeding with warfarin. NSAIDs may aggravate hypertension and antagonizes the effect of antihypertensives, *i.e.* angiotensin-converting enzyme (ACE) inhibitors. NSAIDs, when used in combination with selective serotonin reuptake inhibitors (SSRIs), reduce efficacy of SSRIs and increase the risk of adverse GI effects.

Use in pregnancy: NSAIDs are not recommended in pregnancy, especially in third trimester. Though NSAIDs are not direct teratogens, they may cause premature closure of fetal ductus arteriosus and have adverse effect on fetal kidney. They are also linked with premature births and miscarriage.

Aspirin, together with heparin is used in pregnant woman with antiphospholipid syndrome. Indomethacin is used in polyhydramnios as it reduces fetal urine production due to inhibition of fetal kidney blood flow. Paracetamol (acetaminophen) is safe and well-tolerated during pregnancy.

ORAL CONTRACEPTIVE PILLS

There are epidemiological evidence that women using of combined oral contraceptives (COCs) have reduced incidence of endometriosis.[23] COCs have been shown to be effective in treating pain in women with endometriosis.[24] They can be used as first-line therapy for endometriosis with or without NSAIDs.

Mechanism of Action

They reduce menstrual flow and cause decidualisation of endometriotic implants. They decrease cell proliferation and increase apoptosis leading to decreased pain and scarring associated with endometriosis. Empirical treatment, with COC, without first performing a diagnostic laparoscopy can be given to treat pain symptoms suggestive of endometriosis.[25]

They can be taken for long-term during reproductive life and are generally safe, well-tolerated and acceptable by most women. It also decreases the number of bleeding days and dysmenorrhea.

Low-dose, monophasic combined oral contraceptive pills (COCPs) are often used in clinical practice. COCs that use high-dose of progestin are the most effective for alleviating the symptoms of endometriosis.

COC Regimes for Endometriosis

COCs can be used in a cyclic, long cyclic or continuous manner. Previously, cyclic use of COCs as for contraception was common. However, COCs in extended regimes (long-cycle, continuous) are one of the safest,

cheapest, most practical and recommended methods to suppress menstruation, alleviate endometriosis-related symptoms and probably avoid endometriosis progression.[26] Studies have shown that 3 out of 4 women with endometriosis have reduced pain after COCs.[27] A trial of cyclic or long-cyclic COC should be administered for 3 months. If pain is relieved, the treatment is continued for 6–12 months.

Other Routes for Administration of Combined Hormones

Estrogen–progestin hormones can also be delivered by a vaginal contraceptive ring (Nuvaring) or a skin patch (Ortho Evra) that lasts for a week. Vaginal ring releasing 15 µg of ethinyl estradiol (EE) and 120 µg of etonogestrel, was compared with patch which released 20 mg EE and 150 mg norelgestromin daily. When used continuously both were associated with poor control of bleeding. Regarding pain symptoms ring was found to be better than patch.[28]

Postoperative Use of COCs

It can be effective in prevention of recurrence after conservative surgery for endometriosis. Continuous and cyclic oral-contraceptive pills both have comparable effects. The protective effect, however, seems to be associated with the duration of treatment.[29]

In women with infertility with minimal to mild endometriosis suppression of ovarian function by COCs is not effective and should not be given for this indication alone.[30]

Breakthrough bleeding: The most frequently encountered problem is unscheduled 'breakthrough' bleeding or spotting, which usually becomes less frequent, the longer the hormone treatment is taken. Taking the pill at same time a day and avoiding missed pills will help to prevent breakthrough bleeding.

Contraindications

- Hypertension,
- Pre-existing cardiovascular disease,
- History of thromboembolism or pulmonary embolism,
- Cerebrovascular accident,
- Familial factor V Leiden,
- History of migraine with aura, women who smoke, age >35 years, advanced diabetes,
- Liver tumors,
- Hepatic adenoma or severe cirrhosis of the liver,
- Suspected breast cancer,
- Endometrial cancer,
- Unexplained uterine bleeding.

Pregnancy

Postpartum breastfeeding women are also advised not to start COCPs until 4 weeks.

Interactions

After absorption, EE undergoes metabolism in the liver by CYP enzyme, as it metabolizes many drugs.

CYP inhibitors: CYP inhibition occurs within 48 hours and can increase drug concentrations and vascular complications with increased EE levels. Macrolides except azithromycin, azoles, potentially increase the risk of adverse effects of EE, such as vascular disease complications because of increased EE plasma concentration. CYP inducers may take up to 3 weeks, resulting in decreased drug concentrations. Hence, short-term use of CYP inducers generally will not have clinical significance. After the discontinuation of a CYP inducer, the induction may take several weeks to subside, *e.g.* antimycobacterials, antiretrovirals, anticonvulsants (except lamotrigine). These drugs may cause breakthrough bleeding and increased risk of pregnancy. Hence, women need a backup method of contraception for 6 weeks after discontinuing rifampin.[31]

PROGESTOGENS

They are appropriate for patients who do not respond to COCs or have a contraindication

to use estrogen–progestin contraceptives. Progestins are used as a first-line hormonal therapy for endometriosis-related pain, effects of progestins are comparable to other treatment options.

Mechanism of Action

The suggested mechanisms of progestins in resolving endometriosis-related pain are summarized as:[32,33]

- Ovarian suppression.
- Effects on endometrial morphology (decidualization, atrophy and alteration in steroid-receptor–ligand binding).
- Local modulation of immune reaction [suppression of interleukin (IL) 8 production, increase of nitric oxide production, reduction of tumor necrosis factor-α (TNF-α) induced nuclear factor-χ-β].
- Suppression of the matrix metalloproteinases, which enable the implantation and progression of ectopic endometriotic implants.
- Inhibition of the proliferation of endometrial stromal cells.
- Angiogenesis [suppression of transcription of basic fimbroblast growth factor (bFGF), suppression of vascular endothelial growth factor (VEGF) and cysteine rich angiogenic inducer (CYR61)].
- Progesterone receptor expression and progesterone resistance.
- Direct effect on nerve fibers. Progestins and COCs were found to decrease nerve fiber density and nerve growth factor receptor p75 expression in peritoneal endometriotic lesions.[34]

When taken for a long-term continuously, progestogens tend to thin the endometrium causing amenorrhoea and has similar activity against endometriosis lesions, resulting in their regression. Amenorrhoea induced by high doses of progestins can last many months after stopping therapy, hence, these drugs are not recommended for women planning pregnancy immediately following cessation of therapy.

Routes of Administration

Progestogens can be used to treat endometriosis by various routes, including oral, injections, subdermal implants and intrauterine system.

Choice of progestogen-medroxyprogesterone acetate (provera), norethindrone acetate, and norgestrel acetate, are more potent progestins and are recommended in endometriosis management.

Dienogest (DNG), a newer progestin has gain popularity in medical management of endometriosis. Long-acting progestin-only contraceptive methods, may also be useful in treating endometriosis, *i.e.* injectable medroxyprogesterone (Depo-provera) and levonorgestrel intrauterine device (mirena).

Dose

Refer **Table 44.2** for dosages. Treatment should be continuous and therefore, the dose has to be adapted individually in such a way that amenorrhea is acheived. This is essential for elimination of pain symptoms, and also to prevent progression of endometriosis and presumably to attain regression.

Medroxyprogesterone acetate: It is effective in endometriosis-related pain suppression in both the oral and injectable depot preparations. Breakthrough bleeding can occur with prolonged use.

Depot medroxyprogesterone acetate (DMPA) reduces endometriosis-associated pain as effectively as leuprolide with significantly less bone-mineral density (BMD) decline.[35] Time for resumption of ovulation is longer. Common indications of DMPA is residual endometrosis after hysterectomy when future fertility and irregular bleeding are not the concerns. When used long-term DMPA is detrimental to BMD.

Norethindrone (norethisterone) acetate is a commonly used C-19 nortesterone derivative. It should be continued for 6 to 9 months or until the occurrence of breakthrough bleeding.

Table 44.2: Various progestogens used in endometriosis

S. No.	*Name of progestin*	*Route of administration*	*Dosage*	*Comment*
1.	Norethindrone acetate	Oral	2.5–5 mg, daily	Approved by US-FDA for (2.5 mg) endometriosis
2.	Medroxyprogesterone acetate	Oral	10–40 mg, daily	
3.	Megestrol acetate	Oral	40 mg, daily	
4.	Cyproterone acetate	Oral	10–12.5 mg, daily	Side effects limit its use
5.	Depot medroxy-progesterone acetate	Intramuscular	150 mg, 3 monthly	
6.	Depot mdroxy-progesterone acetate	Subcutaneous	104 mg, 3 monthly	Approved by US-FDA for endometriosis
7.	LNG intrauterine device	Intrauterine device	52 mg, releases 20 µg LNG daily	Effective for 5 years
8.	Etonogestrel	Subdermal implant	68 mg in single rod	Effective for 3 years
9.	Dienogest	Oral	2 mg, daily	Approved by European union

LNG: Levonorgestrel; US-FDA: United States Food and Drug Administration

Megestrol acetate has been also used with similar good results.[36]

Cyproterone acetate (CPA) is a C-21-progestogen derivative. It is an anti-androgen with weak progestational activity. Continuous administration has been found comparable to oral contraceptive (desogestrel and ethinyl estradiol) when used for 6 months in treatment of endometriosis in terms of pain and quality-of-life.[37] The main drawback depression, decreased libido, hot flushes and vaginal dryness limits its generalized use.

DNG is a C-19-nortestosterone progestogen derivative. It has an antiandrogenic and a weak antigonadotropic action. It also has a local antiproliferative and anti-inflammatory effect on endometriotic lesions. It is well- tolerated.

A favorable efficacy and safety profile has been observed with long-term dienogest use, in terms of progressive decreases in pain and bleeding. The decrease of pelvic pain persists for at least 24 weeks after stopping treatment.[38]

Safety profile of DNG: DNG, 2 mg is well-tolerated, with a favorable safety profile even after administration of dienogest for up to 5 years. A progressive decrease in adverse effects and bleeding irregularities occur with low discontinuation rates. The most commonly reported adverse events are headache, breast discomfort, depressed mood, and acne, each occurring in <10% of patients, which were generally mild-to-moderate in intensity.

- *BMD:* A small decrease of 0.5% to 2.7% BMD in the lumbar spine after 1 year of DNG use has been observed in 20–75% of study populations with partially recovery by 6 months after stopping treatment. Changes in BMD should not prevent long-term use of dienogest in women with endometriosis. Women already predisposed to osteoporosis, *i.e.* chronic steroid use, previous fragility fractures, smoking, and malabsorption conditions should be advised about the risks of decreased BMD.

- *Bleeding irregularities:* Treatment with dienogest, 2 mg, as with other progestins, leads to endometrial regression and bleeding irregularities. Initial bleeding during the first 3 months occurs in 80% patients,[39] typically lasting for 8–10 days, with decrease in intensity and frequency over time. In addition, spotting can occur with long-term dienogest treatment. Patients should be counselled for possible bleeding.

Initial irregular bleeding may be reduced by a regimen involving gonadotropin-releasing hormone followed by long-term dienogest therapy. Furthermore, initiation of dienogest 2 mg at the onset of menses may also decrease initial bleeding. Bleeding that occurs during long-term treatment is typically spotting. If the sonographic endometrium thickness is low, management can include a treatment break of 5–7 days to allow for the recovery of the atrophic endometrium, or a short-term use of 1 mg oral or transdermal estradiol (5–7 days). If abnormal uterine bleeding persists, further investigations are required for other uterine pathologies beyond endometriosis.

Subdermal implants: Etonogestrel contraceptive implant/implanon—68 mg in single rod with a life span of 3 years, have been found to be equally effective compared with DMPA in pain relief in 12 months use.[40] It is a safe, well-tolerated for the treatment of endometriosis and achieving long-term contraception.

Levonorgestrel-releasing intrauterine system (LNG-IUS) has been shown to reduce endometriosis-associated pain. Main advantages of the vaginal route include avoidance of the hepatic-first pass metabolic effect, use of lower therapeutic doses and reduced systemic side effects compared to oral administration. When inserted at the time of laparoscopic surgery, it has been found to reduce the recurrence of dysmenorrhea by 35%. This device has improved patient compliance over the once-daily oral progestin formulations because there is no repeated administration.

Adverse effects of progestogens include weight gain, fluid retention, breast tenderness, depression, and breakthrough bleeding. Irregular or unscheduled 'breakthrough' bleeding usually becomes less frequent the longer the medication is used.

Because a chronic disease needs a long-term or intermittently repeated medication clinicians should take the different side-effect profiles of progestagens into account when prescribing these drugs.

Further studies are necessary to clarify the length of treatment, type of progestin, dosage used, intermittent medication and combinations with other drugs, effective in the reduction of endometriosis.

GnRH AGONISTS

Mechanism of Action

The GnRH analogues cause constant stimulation of the pituitary receptors, leading to downregulation and eventual suspension of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion and hypoestrogenic state. Because endometrial implants are dependent on estrogen stimulation, they regress. GnRH agonists also enhance apoptosis and decrease cellular proliferation in the endometrial cells.

The initial surge of LH and FSH may exacerbate endometriosis pain because of the ovarian stimulation. However, 2 weeks after initiation of therapy, an estrogen-deficient state occurs. Women should be counselled about 'flare up' of symptoms and irregular bleeding shortly after they receive their first dose of medication. Later, low estrogen levels may contribute to hot flashes and cessation of periods and other symptoms. GnRH therapy offers high rates of pain relief in 85–100% of women and longer symptom-free period for up to 12 months.[41] Combined with surgery (given perioperatively), a higher cure rate and lower rate of recurrence is seen. Though fertility rates may show no improvement.

Table 44.3: Dosage of GnRH agonists used for endometriosis

Name of GnRH agonist	*Dose*	*Route*
Leuprolide acetate	3.75 mg, monthly	Injectable SC/IM
	11.75 mg, every 3 months	Injectable SC/IM
Goserelin	3.6 mg, every 28 days	SC Injectable implant
	10.8 mg, every 3 months	SC injectable implant
Triptorelin	3.75 mg, every 4 weeks	Intramuscular
Buserelin	2 sprays in each nostril 8 hourly (total 900 µg daily) Nasal spray 1 mg/ml	
	200–500 µg daily	Subcutaneous injection
Nafarelin	One spray into one nostril in morning, and one spray into other nostril in evening daily (total 400 µg daily). May increase to 1 spray in each nostril, twice daily	Nasal spray as 2 mg/ml

SC: Subcutaneous; IM: Intramuscular

Dosage

For dosage of commonly used GnRH agonists refer to **Table 44.3**.

Adverse Effects

Secondary to hypoestrogenism, like bone loss, vaginal atrophy and dryness, hot flashes and abnormalities in lipid profile are encountered.[42] Accelerated bone loss can occur in patients treated long-term with these agents. Six-months duration is the maximum duration. Loss of trabecular bone density caused by GnRH is restored by 2 years after cessation of therapy.[43] Careful consideration in young women and adolescents, since these women may not have reached maximum bone density.

Add-back Therapy

Prevents osteoporosis and hypoestrogenic symptoms. Hormone replacement therapy preparations, progestins, tibolone maleate, and bisphosphonates have all been shown to be effective.[44–46] It prevents loss of bone density and helps to reduce vasomotor symptoms without reducing the efficacy of GnRH. Norethindrone acetate, a progestin is the only Food and Drug Administration (FDA) approved add-back therapy, but low-dose estrogen or a combination of estrogen and progestin have also been used.[47] The combination of GnRH agonists and norethindrone acetate use is approved only for 12 months.

Limitation

GnRH-agonist therapy can be used only for 6 months or 12 months with add-back therapy. As they suppress ovulation, therefore, GnRHa cannot be used in women desiring fertility.

GnRH ANTAGONISTS

GnRH antagonists are being studied as possible management option for endometriosis. These drugs differ from GnRH agonists in that instead of downregulation, there is a competitive blockade at the pituitary GnRH receptor. Gonadotropins are suppressed without the initial flare of estrogen.[48] This suppression of gonadotropins and estrogens is dose-dependent. This inhibits endometriotic cell proliferation and invasion while maintaining sufficient circulating estradiol levels to avoid vasomotor symptoms, vaginal atrophy, and bone demineralization. GnRH antagonists are available as injectables (ganirelix, cetrorelix) and increasingly as oral

nonpeptide forms (elagolix, abarelix, ozarelix, TAK-385).

Elagolix is an oral GnRH-receptor antagonist, approved by the FDA in July 2018 for management of moderate-to-severe pain associated with endometriosis. A dose-dependent improvement of dysmenorrhea is reported. Improvement in noncyclic pelvic pain was also found to be significant.[49]

Elagolix may be considered for premenopausal women with very severe endometriosis associated pain and/or severe endometriosis-related dyspareunia, who have not responded to or have intolerable side effects with first-line treatments (*e.g.* NSAIDs, combined hormonal contraceptives, and progestins), and in whom other causes of pelvic pain have been ruled out. It may also be an appropriate first-line therapy for those with a history of side effect from contraceptive agents.[50]

Treatment with elagolix should be initiated at the lowest effective dose starting from 150 mg once daily. Elagolix 200 mg twice daily is recommended for patients in whom dyspareunia is the main symptom and may be considered for patients with severe non-menstrual pelvic pain. Subsequent transition to 150 mg once-daily dose can be done.

Contraindications

Elagolix is not recommended for patients with a history of nonresponse to GnRH agonists or antagonists, and is contraindicated in women who are pregnant, have known osteoporosis, or have severe hepatic impairment.

Advantages for elagolix are convenient oral therapy, immediate suppression of pituitary gonadotrophs, avoiding the initial 1–2 week flare-up effect of GnRH agonists, dosage can be individualized according to symptom severity. Vasomotor symptoms are mild-to-moderate and not as severe as seen with GnRH-agonist treatment. Further studies are needed to determine if add-back therapy might help to alleviate mild-to-moderate hypoestrogenic side effects.

Cetrorelix: Administration of 3 mg weekly dose of cetrorelix for 8 weeks can be a feasible medical option for endometriotic pain. In a study, it was reported that all women (100%) had pain-free period during treatment with cetrorelix.[48]

Adverse Effects

GnRH antagonists—hypoestrogenic adverse effects include hot flushes, elevated serum lipids. Decreases in bone mineral density is more compared to placebo treatment but less compared to GnRH agonists. Frequency of hot flushes with elagolix was found to be lower than that with leuprolide acetate.

AROMATASE INHIBITORS (AIs)

A more current approach to the treatment of endometriosis has involved the administration of drugs known as aromatase inhibitors, *e.g.* anastrozole and letrozole.

Mechanism of Action

Estrogen is the major biochemical driving force for endometriotic implant growth. Besides ovaries, evidences indicate the expression of P450 aromatase enzyme by endometriotic implants which are an intracrine source of estrogen.[51] This enzyme is involved in the conversion of androstenedione to estrone and testosterone to estradiol (E_2). As a result, emphasis has been placed upon the use of aromatase inhibitors (AIs) to curtail production of estrogen by endometriotic implants and subsequent implant growth. These drugs act by inhibiting local estrogen formation within the endometriosis implants. They also inhibit estrogen production within the ovary and adipose tissue.

The most potent, selective, and reversible are the third-generation AIs, which are commonly used, *e.g.* letrozole and anastrozole. The third-generation AIs decrease serum 17β-estradiol by 97–99% as early as 24 hours after dosing. They also increase FSH levels in premenopausal women.

AIs in Pre-menopausal Endometriosis

Standard management, such as GnRH analogues, which effectively downregulates ovarian E_2 (estradiol) biosynthesis, has little impact on extraovarian E_2 production. However, AIs downregulate extraovarian E_2 synthesis, which in turn stimulates ovarian E_2 production through initiation of the FSH surge. Accordingly, AIs are combined with standard regimes to suppress both ovarian and extraovarian E_2.

AIs have been beneficial and effective therapy for premenopausal patients with chronic pelvic pain, after prior conservative surgery, used for 3 to 6 months whether given alone or in combination with oral contraceptives/progestins/GnRH. It has also been used in ovarian endometriosis, *i.e.* bladder endometriosis, colorectal endometriosis with good results. Use of postoperative AIs with GnRHa for 6 months reduced the risk of recurrence of endometriosis when compared with GnRHa alone.[52]

AIs should only be administered to patients who failed to respond to conventional therapies (such as progestins and/or oral contraceptives) and do not want surgical removal of disease.

AIs in Postmenopausal Endometriosis

Aromatase inhibitors (AI) are being considered as potential treatments for postmenopausal endometriosis as most of the body's estrogen is produced outside the ovaries after menopause which is suppressed by AIs.

The incidence rate of endometriosis is 2–5% in postmenopausal women. Surgery is preferred over non-surgical treatment in these patients due to the risk of cancer development. However, recurrence of endometriosis even after surgery can occur. Moreover, all older patients are not eligible for surgery. In these women with endometriosis, treatment with letrozole and anastrozole for 4–15 months reduced pain.[53] Letrozole also decreased urinary and gastrointestinal tract symptoms associated with endometriosis. AIs have been used in recurrent severe endometriosis after hysterectomy and bilateral salpingo-oophorectomy, resulting in a significant reduction in pelvic pain and lesion size.

Aromatase Inhibitors in the Treatment of Infertility Caused by Endometriosis

In infertility caused by endometriosis, medical treatment with hormones is not effective and not indicated. It has been observed that intrauterine insemination (IUI) with controlled ovarian stimulation (without surgery or within 6 months of surgery) may be effective in patients with mild-to-moderate endometriosis.[54,55] Letrozole is administered at a dose of 2.5–7.5 mg/day on days 3–7 of the menstrual cycle for ovulation induction. Compared to clomiphene, letrozole inhibits oestradiol synthesis rather than its oestrogenic activity and has no anti-oestrogenic effect on cervical mucus or endometrium.

Dosage: Letrozole—2.5 mg/day for 3–6 months; anastrozole—1 mg/day for 3–6 months.

Side effects of the third-generation AIs include vaginal dryness, hot flushes, headache, back pain, numbness in lower extremities, and arthralgia, irregular bleeding.[56] Its long-term use is associated with increased risks of osteoporosis and fracture rate owing to diminished BMD.[57] For these reasons, aromatase inhibitors and may be given concurrently with combined estrogen-progestin contraceptives or progestins for management of endometriosis. Also, vitamin D or bisphosphonates are sometimes added to AI therapy.

Long-term monotherapy with aromatase inhibitors when given to reproductive-age women will cause increased FSH levels and subsequent superovulation, resulting in ovarian cyst development due to the initial FSH rise.

Treatment of endometriosis by AIs is reserved for severe, intractable endometriosis-associated pain in combination therapy with

Table 44.4: Medical options priority-wise for various symptoms related to endometriosis

Medication	*Indication*	*Priority*	*Adverse effects*
NSAIDs	Dysmenorrhea	First	Nausea, vomiting, GI irritation, vertigo
COCs			
COCs cyclic	Dysmenorrhea	First	Nausea, weight gain, water retention, depression, breast tenderness, headache, intercyclic bleeding, decreased menstrual bleeding
COCs continuous	Dysmenorrhea, non-cyclic chronic pelvic pain	First or second	Nausea, weight gain, water retention, breast tenderness, headache, amenorrhea, breakthrough bleeding
Progestins			
MPA, NETA DNG, CPA	Dysmenorrhea, non-cyclic chronic pelvic pain	First or second	Nausea, weight gain, water retention, breast tenderness, headache, amenorrhea, breakthrough bleeding, delay in regulation of menstrual pattern
LNG-IUS	Dysmenorrhea, dysparunia, recto-vaginal endometriosis	Second or third	Bloating, weight gain, headache, breast tenderness
GnRH agonists	Dysmenorrhea, dysparunia,	Second or third	Hypoestrogenism (hot flushes, vaginal dryness, irritability), decreased BMD
*Aromatase inhibitors	Dysmenorrhea, non-cyclic chronic pelvic pain	Third	Hypoestrogenism (hot flushes, vaginal dryness, irritability), ovulation induction
Danazol	Dysmenorrhea, non-cyclic chronic pelvic pain	Second or third	Hyperandrogenism (acne, edema, decrease in breast size)

*Aromatase inhibitors should be combined with COCs or GnRHa.

oral contraceptive pills, progestins, and GnRH analogues.

DANAZOL

This agent is a synthetic androgen with minimal estrogen or progesterone potential.

Mechanism of Action

Drug acts by inhibiting gonadotropin secretion and inhibiting steroidogenic enzymes in ovary, preventing midcycle FSH and LH surge and interfering with ovulation and ovarian production of estrogen.[58]

Pharmacokinetics

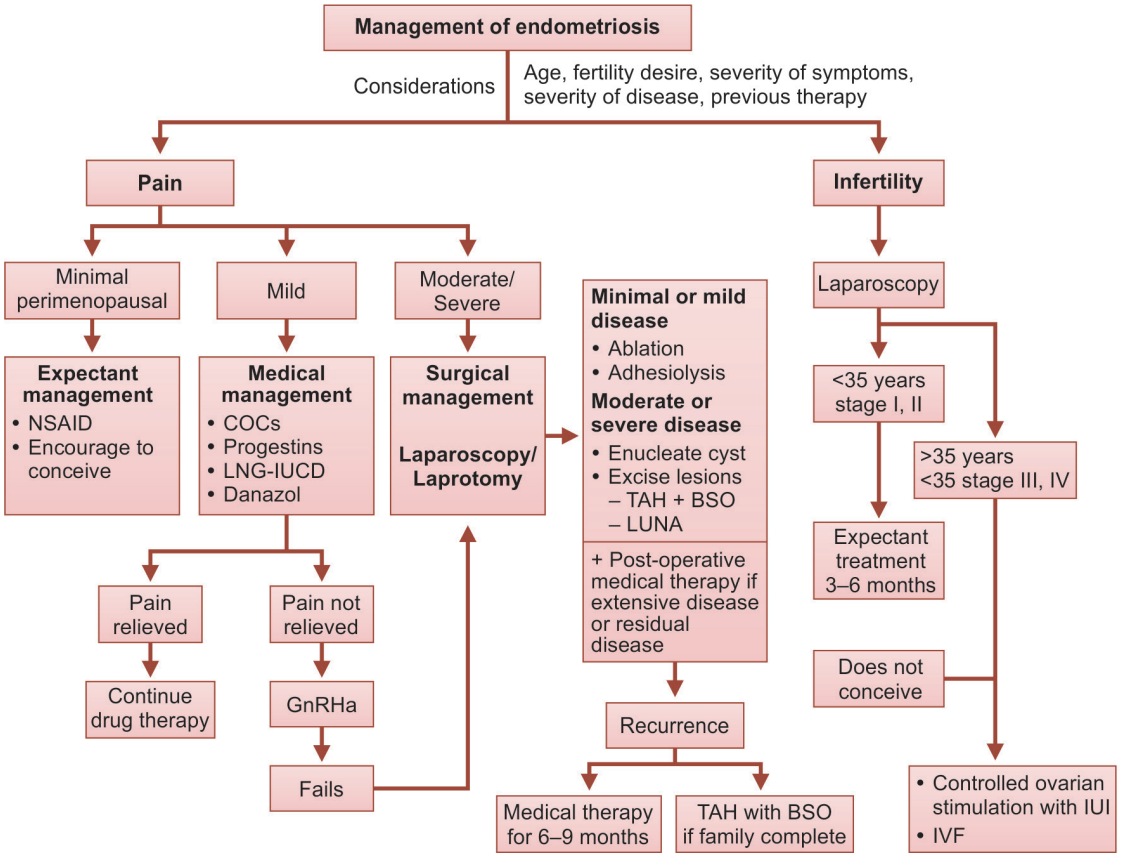
Danazol is well-absorbed from the gastrointestinal system. Peak plasma concentration of danazol is reached within 2 to 8 hours post-oral administration of 400 mg tablet. Danazol is lipophilic and hence has the potential to penetrate deep tissue compartments. Danazol is extensively metabolized in the liver to 2-hydroxymethyl ethisterone. It is mainly excreted in the urine, and a small amount is excreted in the feces.The half-life of danazol has been reported to be at a mean of 9.7 hours.

It is quite extensively studied agent used for endometriosis. Pain relief and shrinkage of endometriosis implants occur in 80% women using danazol.

Dose

Danazol is administered orally in divided doses ranging from 400 mg to 800 mg daily for 6 to 9 months in mild cases; severe cases may require 800 mg per day in two divided doses. However, smaller doses have been used with success.[59,60] In a small study of

Flowchart 44.1: Algorithm for management of endometriosis



21 patients, vaginal danazol (200 mg/d) was successful in relieving endometriosis-associated pain.[61]

Side Effects

Up to 75% of women develop significant side effects from the drug. These include androgenic and hypoestrogenic manifestations: Side effects include weight gain, edema (swelling), breast shrinkage, acne, oily skin, facial hirsutism, deepening of the voice, headache, hot flashes, emotional lability, changes in libido, mood alterations etc. All of these side effects are reversible with exception of voice changes. It may take many months for resolution of the side effects.

Contraindications

Women with liver, kidney, or heart conditions should not take danazol.

Pregnancy: Danazol should not be used in pregnancy. While on danazol therapy, due to possibility of virilizing changes in a female fetus, additional barrier contraception must be used **(Flowchart 44.1)**.

Limitations

The increase in liver injury, androgenic adverse effects, such as acne, hirsutism, and male pattern baldness and risk of thromboembolism limits the use of danazol for endometriosis treatment. The drug has several US-FDA boxed warnings, including the risk of thrombosis and teratogenicity.

NEWER THERAPIES

Endometriosis is a chronic medical condition and requires long-term therapy. Various treatment options available, have varying

degrees of success in symptom control. Many are limited by long-term use, side effects of prolonged hypoestrogenism and high rates of recurrence after therapy is discontinued. Also, endometriosis predominantly is a disease of young reproductive-age women and most of the commonly available therapeutic agents interfere with fertility. Due to these drawbacks there is a constant search for newer therapies that could offer cure and which can be safely used with fewer side effects.

Selective Progesterone Modulators (SPRMs)

SPRM can have a variable effect from different tissues from pure agonist to mixed agonist and antagonist to pure antagonist. Mifepristone have shown to have dose dependent inhibitory effect on endometriotic implants. It was shown to have positive-effects on endometriosis-related pain. It induced amenorrhoea without causing hypoestrogenism.

Ulipristal acetate and asoprisnil also have shown to cause regression of endometriotic lesions. However, in the endometrium, SPRM-associated changes, closely mimicked hyperplasia which developed after less than 3 months of treatment, and resolved after discontinuation of ulipristal and induction of withdrawal bleed. Feasibility of SPRMs is yet to be determined.[62]

Selective Estrogen Receptor Modulators

These have different effects in different tissue types, make them interesting agents for further endometriosis research, *e.g.* blocking estrogen-mediated growth of endometriotic lesions and at the same time supporting bone-mass remediation.

Bazedoxifene (BZD), a third generation SERM, approved for use in menopausal symptoms, has demonstrated to regress endometriotic lesions. Combined with conjugated estrogens has better tolerability and reduced side-effect profile.[63] It represents a potential treatment option for endometriosis. The feasibility, effectiveness of benzedoxifene acetate (BZA) is yet to be evaluated.

Anti-angiogenesis factors: Angiogenesis is crucial for growth and survival of endometriotic lesions. Studies have shown that these lesions secrete angiogenic factors like VEGF. Therefore, anti-angiogenic factors could stop growth of new lesions and regress older ones. This forms the basis of use of anti-angiogenic factors in the treatment of endometriosis. These are still in early development phase. TNP-470, endostatin, anginex and anti-VEGF antibody (Avastin®) have been successful in decreasing the size of endometriotic lesions in animal models, however, no data is available in humans.

Dopamine-receptor-2 agonists, cabergoline and quinagolide reduce angiogenesis by dephosphorylation of $VEGF_2$. Cabergoline has shown better results compared to LHRH-agonist, in reducing the size of endometrioma. It has no major side effects, easy to administer, and cheaper than LHRH agonists.[64] In a study comparing cabergoline and medroxyprogesterone acetate, both were found to be equally effective in decreasing chronic pelvic pain due to endometriosis. Cabergoline had a better acceptance and compliance due to lesser side effects and less frequent dosing. It can be a better alternative to medroxyprogesterone acetate,[65] though enough data is not available to recommend its routine use.

Peroxisome Proliferator-activated Receptor Gamma Ligands (PPAR-γ)

These PPARs are ligand-activated nuclear receptors. PPAR-γ ligands have anti-inflammatory properties and reduce estrogen production by inhibiting aromatase enzyme. In experimental models, they have been shown to inhibit cell proliferation, increase apoptosis and inhibit the growth of the endometriotic lesions through angiogenic factor VEGF. In animal models, rosiglitazone and pioglitazone reduce the volume, weight and size of the endometriotic lesions. Human

studies are underway, however there are concerns about the possible cardiovascular risk.[66]

TNFα Blockers

It is a pro-inflammatory cytokine and its levels have been found to be elevated in the peritoneal fluid of women with endometriosis with a direct correlation with the stage of the disease. Infliximab, a monoclonal antibody against TNFα, has shown to reduce the size and number of the endometriotic implants and decrease in the levels of inflammatory cytokines in animal models. In a study on infliximab *vs* placebo in women with endometriosis, no improvement was reported in the severity of pain.[67] There is lack of evidence in humans regarding the efficacy of these agents.

Statins

These drugs, e.g. atorvastin, simvastin, lovastin, etc. lower cholesterol levels by blocking the conversion of 3-hydroxy-3-methylglutaryl- coenzyme-A into mevalonate, which is a precursor of cholesterol. Their anti-inflammatory, antiangiogenic and antioxidant properties have provoked interest in their use for endometriosis. Only lipid-soluble statins were effective in inhibition of growth and invasiveness of human endometrial cells in a *in vitro* study. Though evidence support statins as the potential therapeutic agent for conservative treatment of endometriosis, yet, the uncertainties regarding their impact on gonadal function may deter its use as an appropriate therapy for all young fertile women.[68]

Romidepsin

An anticancer drug used in cutaneous T-cell lymphoma, targets VEGF at transcriptional level, which cause reduction in secretion of VEGF from human immortalized epithelial cells. Therefore, romidepsin may be a potential therapeutic agent against angiogenesis in endometriosis. Unlike other antiangiogenic treatments that can only target developing angiogenesis, romidepsin eliminates pre-existing pathologic vessels. Consequently, romidepsin could serve as a novel, fertility-preserving, and effective treatment for endometriosis.[69]

Pentoxyphylline

It is a methylxanthine with anti-inflammatory property, acting as a phosphodiesterase inhibitor, that has been proposed for treating endometriosis. In a prospective RCT designed to test the effect of oral pentoxifylline combined with laparoscopic surgery on pelvic pain, reduction in pain scores was documented most significantly.[70]

Nanotechnology

Some fundamental principles of cancer nanomedicine can potentially be used for the development of novel nanoparticle-based strategies for treatment and imaging of endometriosis. Finding of nanoparticles that can predominantly accumulate in endometriotic lesions without toxic effect on the body, while preserving their imaging and heating properties is a challenge. The heat generated ablates the endometrial lesions completely within a day or two. Strategy can eventually shift the current paradigm for endometriosis detection and treatment.[71]

SUMMARY

For the treatment of endometriosis, diverse therapeutic approaches, including no treatment, medical treatment, surgical treatment, and a combination of medical and surgical treatment, have been used. Medical treatment consists of hormonal therapy that most commonly includes combined oral contraceptives, high-dose progestins, danazol, and GnRH agonists. The basis of pharmacologic therapy is that endometriosis implants are capable of responding to hormones. NSAIDs may be considered in patients with mild symptoms and can be combined with hormonal therapy. However,

none of these treatments eradicates the disease, they are associated with side effects. Sometimes, endometriosis-related symptoms reappear after therapy is discontinued. GnRH analogues, danazol, and depot progestagens are associated with a higher incidence of adverse events. Hormonal management is not suitable for woman suffering from endometriosis who wish to get pregnant and severe symptoms or severe disease (stage III, IV). AIs can be given in intractable cases along with COCs or progestins.

As long term treatment and repeated treatment is required, choice of treatment depends on efficacy, adverse side effects, long-term safety, cost, and availability of the drug.

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Chapter

45

Genital Tuberculosis: Medication with Case-Based Approach

• Sujata Dalvi

Introduction

Female genital tuberculosis is an important cause of infertility. Its incidence in India varies from 3 to 16%. The fallopian tubes are involved in 90–100%, endometrium 50–80%, ovaries 20–30% and cervix 5–15% of cases.[1] It occurs secondary to pulmonary or extrapulmonary TB, like gastrointestinal (GI) tract because of hematogenous/lymphatic spread. Diagnosis is made by actual visualization of lesions-adhesions on laparoscopy/hysteroscopy followed by biopsy of suspicious lesions. Histopathology report of endometrial tissue/lesion, positive culture for acid-fast bacillus (AFB) or positive *Mycotracterium tuberculosis*-polymerase chain reaction (TB-PCR) test are also methods of diagnosis. However, high degree of suspicion is required.

There is increased incidence of tuberculosis in developing countries and it may be co-existent with human immunodeficiency virus (HIV).

Antituberculosis drug regime is 3 or 4 drug combination [antitubercular treatment (ATT)]. Duration of therapy will be for 9 to 12–18 months. Multidrug resistant (MDR) or extreme drug-resistant TB (XDR) are of concern because of poor drug management. World Health Organization (WHO) declared TB a global emergency in 1993 and promoted directly observed treatment short course (DOTS) strategy. DOTS has 70% detection and 85 % successful treatment rates.

MEDICAL THERAPY

National Institute of Clinical Excellence (NICE)/American Thoracic Society/British Thoracic Society guidelines recommend first choice of treatment to be 'standard recommended regime' using daily dosing schedule with combination tablets. Those who can adhere to treatment, DOTS is not necessary. However, DOTS is recommended by WHO.

WHO Recommendation

Daily therapy of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for 2 months followed by daily rifampicin (R) and isoniazid (H) for 4 months

- Weight <45 kg (2 HRZE—300/450/1250/800)
- Weight >45 kg (2 HRZE—300/600/1750/1200)

Or

- 2 months intense therapy of RHZE daily, followed by alternate days combination of RH for 4 months.

Or

- 3 times a week dose of (2 RHZE)/(4RH) throughout therapy, provided patient

is under direct observation and is HIV negative.

Or

- Continuation phase daily (4 months)—3-drug-fixed-dose combination after intense therapy of 2 months
- Weight <45 kg (4 HRE—300/450/800)
- Weight >45 kg (4 HRE—300/600/1200)
- 4-Drug fixed dose combination (FDC)—HRZE (75/150/400/275)

Therapy is given after categorizing patient to one of the treatment regimes. Genital TB is classified as category 1, as seriously ill extra-pulmonary disease. To ensure adequate dose with quality control, 6-month course pack box is booked in DOTS center with fixed-drug combipacks (FDC) of isoniazid, rifampicin, pyrazinamide and ethambutol, three times a week for first 2 months (intensive phase) followed by combination pack of isoniazid and rifampicin, three times a week for next 4 months (continuation phase).

Female genital tuberculosis (FGTB) cases with relapse or failure are included into category II. The regime has streptomycin injections, intramuscular, three times a week for 2 months with other four drugs (SRHZE) of category I, followed by four drugs (RHZE), three times a week for 1 month (intensive phase) then continuation phase with three drugs isoniazid (H), rifampicin (R) and ethambutol (E), three times a week for next 5 months.

Multidrug Resistant/Probable Multidrug Resistant

Intensive phase, daily (6–9 months):

- Body weight <45 kg—kanamycin (IM) 500/levofloxacin (O)—500/ethionamide (O) 500 / cycloserine (O) 500/pyrazinamide (O) 1250/ ethambutol (O) 800
- Body weight >45 kg—kanamycin (IM) 750/levofloxacin (O) 750/ethionamide (O) 750 /cycloserine (O) 750/pyrazinamide (O) 1750/ethambutol (O) 1200

Continuation phase daily (18 months):

- Weight <45 kg—levofloxacin (O) 500/ethionamide (O) 500/cycloserine (O) 500/ethambutol (O) 800
- Weight >45 kg—levofloxacin (O) 750/ethionamide (O) 750/cycloserine (O) 750/ethambutol (O) 1200
- Moxifloxacin to be given—resistant to levofloxacin

Treatment of chronic and multidrug resistant (MDR) FGTB is similar to that for pulmonary MDR with second-line drugs for 18–24 months.

Pregnancy:

For latent tuberculous infection (LTBI)—isoniazid 300 mg with pyridoxine 25 mg, daily for 6 to 9 months. HIV positive—to start immediate treatment. Those on antiretroviral therapy (ART)/HIV negative—defer treatment till postpartum if no risk factors.

Rifampicin, isoniazid, pyrizinamide are safe during pregnancy.

Active TB during pregnancy—INH, RIF, pyrizinamide and ethambutol (EMB) given for 2 months followed by INH, RIF for next 4 to 7 months daily with pyridoxine supplementation. Monitoring of hepatic function is recommended. Newborn to receive INH for 6 months followed by bacillus calmette-Guerin (BCG) vaccine after ruling out active TB. Vitamin K to be given to newborn if mother is on rifampicin.

Non-DOTS Treatment

Patients not opting for DOTS, should take RHZE daily for 2 months (intensive phase) followed by RH for 4 months (continuation phase). Combipacks are available at reasonable cost.

Monitoring

Counselling is necessary for the importance of taking AKT regularly with good/nutritious diet and reporting any side effects. Liver function tests to be done only for symptoms of hepatic toxicity. Pyridoxine should be

prescribed with AKT only with symptoms of peripheral neuropathy with isoniazid. Occasionally, hepatitis is seen with isoniazid, rifampicin and pyrazinamide, optic neuritis by ethambutol and auditory/vestibular toxicity by streptomycin. In these cases, modified form of AKT can be restarted after expert opinion.

Adverse effects: First-line medications are safe. There are minor side effects. Rarely, serious ones like hepatitis can occur. The side effects are as follows:

- Isoniazid—peripheral neuropathy, seizures, erythema, hepatitis, lethargy Rifampicin—hepatitis, skin reaction, arthritis, thrombocytopenic purpura.
- Pyrazinamide—hepatitis, GI irritation, nausea, vomiting
- Ethambutol—optic neuritis

Reserve drugs:

- Streptomycin/kanamycin—ototoxicity, renal problems, vertigo
- Quinolone derivatives/ethionamide—GI irritation, abdominal pain, vomiting
- Cycloserine—neurological like dizziness, seizures, headache, tremors

Treatment of FGTB in HIV-Positive Women

HIV has serious impact to control TB and is leading cause of HIV-related morbidity and mortality. In India, Revised National Tuberculosis Control Program (RNTCP) and National AIDS Control Organization (NACO) together have devised protocol for proper management of this dual epidemic. The options for antiretroviral therapy in TB patients are:

- Defer antiretroviral therapy until completion of TB treatment
- Defer antiretroviral therapy until end of initial phase of treatment and usage of ethambutol and isoniazid in continuation phase
- To treat TB with rifampicin-containing regimen with efavirenz and 2 nucleoside reverse transcriptase inhibitors (NRTIs)
- Treat TB with rifampicin-containing regimen with 2 NRTIs and then change to maximally suppressive highly active antiretroviral therapy (HAART) regimen on completion of TB treatment.

NEW TB RESEARCH

Globally, there is renewed interest in research in TB. Improvised new BCG vaccines are being developed. Newer drugs, effective against resistant strains and requiring shorter treatment are being developed. WHO recommends Xpert MTB/RIF rapid screening test for resistant strains with simultaneous detection of TB (<2 hours), where culture takes 3 to 6 weeks. Injection-free regimen using bedaquiline and delamanid have been recommended by WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment (2019).[2] WHO rapid communication has recommended injection-free regimens for all types of TB, including MDR and rifampicin-resistant (RR) TB... By controlling TB, FGTB can be under control to prevent complications.

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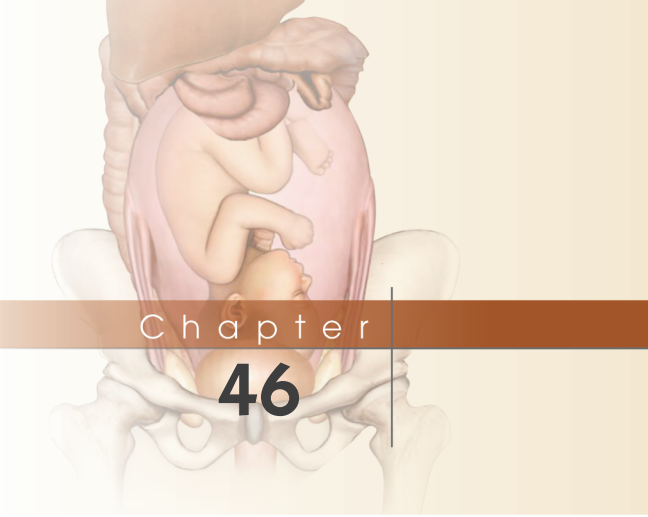

Chapter
46

Hyperprolactinemia

• Ritu Bharadwaj • Ruchika Garg

Introduction

Serum prolactin (PRL) concentration in normal adult males and females is less than 14 µg/L and 24 µg/L, respectively (PRL conversion units: 1 µg/L = 21.2 mU/L). The reported reference ranges for total PRL on the Abbott Architect assay is 2.7–19.7 µg/L for males and 3.0–26.4 µg/L for females. Serum PRL is unaffected by food and a fasting sample is not necessary. Hyperprolactinemia causes galactorrhea-amenorrhea-infertility syndrome in women. Prolactin causes inhibition of gonadotropin-releasing hormone (GnRH) which leads to inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion.

SIGN AND SYMPTOMS OF HYPERPROLACTINEMIA

- Menstrual disturbances like oligo-menorrhea, amenorrhea, menorrhagia
- Infertility
- Galactorrhea and as hypogonadotropic hypogonadism like decreased libido, impotence, infertility, oligospermia or gynecomastia, erectile dysfunction or galactorrhea (rare) in men.
- Sign and symptoms caused by mass effect are headache, visual field defect or external ophthalmoplegic.

Symptoms of hyperprolactinemia depend upon the magnitude of prolactin elevation as

- Serum prolactin greater than 100 ng/dl will have overt hypogonadism with the presentation of amenorrhea, hot flashes, and vaginal dryness.
- Serum prolactin between 50 ng/dl to 100 ng/dl may cause amenorrhea or oligomenorrhea.
- Serum prolactin 20 to 50 ng/dl may only shorten the luteal phase because of insufficient progesterone secretion.

There are physiologic causes for a rise in PRL, such as pregnancy, lactation, physical exertion or stress. During pregnancy, PRL increases in response to increasing estradiol ranging from 35–600 µg/L. PRL is not increased in non-lactating women and men after nipple stimulation or breast imaging and breast examination.

The causes of hyperprolactinemia are prolactin-secreting tumours which may be micro or macroprolactinoma.

A microadenoma is described as having a maximum diameter of up to 10 mm (the maximal diameter of the normal pituitary gland) while a macroadenoma has a diameter larger than 10 mm. Giant adenomas are defined as the presence of the largest diameter of the tumor being larger than 4 cm.[18] A microadenoma is often visualized

using magnetic resonance imaging (MRI). Usually, the serum prolactin level is below 200 ng/ml (4000 mU/L) in patients with microadenomas. A macroadenoma that secretes prolactin is usually associated with a serum prolactin level of more than 200 ng/ml (4000 mU/L). If the patient has a macroadenoma and a serum prolactin level of less than 200 ng/ml (4000 mU/L), possibility of a nonfunctioning pituitary adenoma (pseudo-prolactinoma), resulting from deprivation of some lactotrophs of dopaminergic inhibition is there.

Other causes include hypothalamic disorders, like craniopharyngioma, suprasellar pituitary mass extension, meningioma, dysgerminoma, hypothalamic metastases weakening its inhibitory control over pituitary.

DRUGS CAUSING HYPERPROLACTINEMIA

Antipsychotic (dopamine receptor-blocking agents) risperidone, haloperidol, fluphenazine, etc. antiemetic (dopamine receptor-blocking agents), metoclopramide, domperidone and prochlorperazine.

MEDICAL CONDITIONS CAUSING INCREASED PROLACTIN

Chronic Renal Failure

Polycystic ovarian disease (PCOD), liver cirrhosis, pseudocyesis, primary hypothyroidism, ectopic production in bronchogenic carcinoma and hypernephromas and may be idiopathic.

Prolactin is under predominant inhibitory control of hypothalamus through prolactin release-inhibiting hormone (PRIH) which is dopamine that acts on pituitary lactotrophs D_2 receptor. Thus, dopaminergic agonist, such as bromocriptine, cabergoline decrease plasma prolactin.

DIAGNOSIS OF PROLACTINOMA BY IMAGING

MRI allows accurate measurement of the size of the pituitary and of any tumor, and its relationship to the optic chiasm and cavernous sinuses. Cisternal herniation is also readily seen. If MRI is not available, computed tomography (CT) scanning is also helpful, but the resolution is less good and it is less satisfactory for delineating the relationship of the diaphragm sellae with the optic chiasm. There is little place for routine skull X-ray other than for delineating bony structures.[26]

PROLACTIN INHIBITORS USED IN TREATMENT OF HYPERPROLACTENEMIA

1. Bromocriptine

Bromocriptine is a synthetic ergot derivative which is a potent dopamine agonist. It has its greater action on D_2 receptors and it decreases prolactin release from pituitary, while at certain dopamine sites in the brain, it acts as a partial agonist or antagonist of D_1 receptor. It is also a weak α-adrenergic blocker. Bromocriptine is preferred during pregnancy because of more favorable data than cabergoline.

Side effects: Nausea, vomiting, constipation. Postural hypotension may be marked at initiation of therapy. Syncope may occur if starting dose is high. Hypotension is more likely in patients taking antihypertensive, etc. Behavioural alterations, mental confusion, hallucinations, psychosis, etc. are other rare side effects.

Pharmacokinetics:

Bioavailability—28% of oral dose absorbed

Metabolism—extensively liver-mediated

Elimination—half-life 12–14 hours

Excretion—85% bile (feces), 2.5–5.5% urine.

Dosage: For initiation of therapy, dosage is 1.25–2.5 mg, once a day. Dosage may be increased up to a dosage of 15 mg, once a day, according to the patient's serum prolactin level.

2. Cabergoline

Cabergoline is D_2 agonist more potent more selective for pituitary lactotrope D_2 receptors. It is the first-choice drug for treatment of

hyperprolactinemia. Serum prolactin levels fall to the normal range in 2–4 weeks and in many women it is found that they conceive within a year.

Side effects: Same as bromocriptine but incidence is lower.

Pharmacokinetics:
Bioavailability—first-pass effect seen; absolute bioavailability unknown.
Protein binding—moderately bound (40–42%), concentration, independent.
Metabolism—hepatic, predominately via hydrolysis of the acylurea bond.
Elimination—Half-life 63–69 hours (estimated), thus cabergoline is longer-acting than bromocriptine.
Excretion—Urine (22%), feces (60%).

Dosage: For initiation of therapy, dosage is 0.25 mg, twice a week. Dosage may be increased up to a dosage of 1 mg, twice a week, according to the patient's serum prolactin level. The dose can be reduced from the typical dose of 0.25 mg, twice a week to 0.25 mg once a week and then to 0.25 mg every other week before discontinuation.

Side effects of dopamine agonist (DA) therapy, usually occur at the start of treatment and frequently disappear with continued therapy. If treatment is started with full doses or increased too quickly, dizziness, nausea, and postural hypotension may occur. To avoid such effects, DA must always be taken during a meal. Administration should be started at night, with a snack, when the patient retires to bed. Doses can be gradually increased afterwards.

Cabergoline and pergolide are associated with a higher risk of cardiac valvopathy in patients with Parkinson's disease.

Note:
- Before initiating treatment for hyperprolactinemia, cardiovascular evaluation should be performed and echocardiography should be considered to assess for valvular disease.
- Dosage increase should not occur more rapidly than every 4 weeks, so that the physician can assess the patient's response to each dosage level.
- If the patient does not respond adequately and no additional benefit is observed with higher doses, the lowest dose that achieved maximal response should be used and other therapeutic approaches considered.
- Patients receiving long-term treatment should undergo periodic assessment of their cardiac status and echocardiography should be get done.
- DA therapy is effective not only in patients with microadenomas, but also in the majority of patients with large prolactin-secreting tumors in reducing tumor size. Moreover, emerging evidence point to the possibility of drug withdrawal after long-term treatment.

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Chapter

47

Current Concepts in Hormone Replacement Therapy: Estrogen and Progesterone

• Priya Vora • Rana Choudhary

Introduction

Menopause is an important transition phase that brings in many changes that can affect the quality of life in a woman.[1] The reproductive morbidity and mortality increase as aging progresses and leads to menopause.[1] Due to gradual decrease in estrogen and progesterone from these aging ovaries, hormone replacement therapy can be used in the form of synthetic progesterone and estrogen to replace a woman's depleting hormone levels, thus alleviating symptoms of menopause and preventing long-term adverse effects on bone, cardiovascular system, and urogenital system.

Hormone replacement therapy underwent dramatic swings during the last 50 years. It was extremely popular before the WHI study. The enthusiasm for HRT was smashed in 2002, after the WHI trial on health costs and benefits of hormonal therapy. Age of the women at starting HRT is extremely important in the beneficial effects of HRT, as it determines its effectiveness as well as side effects. The use of HRT reduced significantly after the results of WHI study (2002). This has lead the scientists and caregivers to look for alternative options in management of perimenopausal and menopausal symptoms. According to this study, postmenopausal on HRT had an increased risk for breast cancer, heart diseases, stroke and clotting tendencies. However, there was no agent/drug which could replace estrogen in terms of providing beneficial effect over various organs and systems as was seen with use of estrogen. However, over these years the fear of using HRT has not reduced among women and clinicians which has resulted in unnecessary anguish. Unfortunately, after the WHI, till date several clinicians do not feel safe prescribing HRT neither are they trained in this. There are many papers which demonstrate the protective effect of HRT in reducing risk of coronary disease, osteoporosis, and dementias when it was started within 10 years of menopause.

NEED FOR HRT

South Korea is predicted to be the number one in the world (by 2030) in terms of life expectancy of women. This is reaching 90.82 years. In a recent study, it is estimated worldwide that 1 billion women by 2020[2] and by 2050 1.6 billion women will reach menopause or be postmenopausal.[3] Indian women have a life expectancy of 72.3 years,[4] with an average age for attaining menopause around 47–49 years. Hence, maintaining a positive post reproductive phase, preventing non-communicable disease, reducing

mortality, and better quality-of-life after menopause is crucial.

Most menopausal Indian women complain of instability in vasomotor system presenting in the form of hot flashes, sweating and palpitations. Urogenital symptoms, like urinary frequency, urgency, vaginal dryness, soreness and dyspareunia are common. Psychological symptoms, such as mood changes, insomnia, depression and anxiety make day-to-day activities difficult. Long-term effects are osteoporosis and cardiovascular disease and Alzheimer's disease. HRT markedly reduces the symptoms of menopause, like vasomotor, vaginal and vulvar dryness, risk of fractures due to osteoporosis and improves quality-of-life.

WORK-UP BEFORE HRT

- History taking and a proper physical examination are imperative.
- Blood pressure needs to be recorded before giving HRT.
- Haemoglobin including complete blood count (CBC), sugar levels, liver function tests, lipid profile, and thyroid profile are the investigations needed to be performed.
- Pelvic ultrasonography, mammography, bone mineral density (BMD) test, Pap smear screening, and endometrial biopsy are also helpful.

TYPES OF HRT

- Hormonal HRT—many women are given a combination of oestrogen and progestogen hormones. However, women who have undergone hysterectomy can take only estrogen without any need for progesterone supplementation.
- These preparations are available in various forms, like tablets, gels, vaginal creams, pessaries or rings and skin patches.
- These medicines used as HRT medicine can be taken continuously or with a small break in between two cycles. In these cases, oestrogen can be used continuously with progestogen added in between.

MECHANISM OF ACTION

Estrogen (steroid hormone) has an important role in the functioning of reproductive system. It acts basically on the uterus and vagina. It changes the transcription of genes in these tissues. This is through the action on certain receptors, like nuclear transcription factors. These nuclear transcription factors regulate the genes by getting attached to the promoter regions in specific genes of the uterus and vagina.

Oestrogen has an important effect on the vaginal pH. This typically ranges between 4.5 and 6.0, in years preceding menopause. Estrogen is responsible for decreasing the pH by its mechanism on the vaginal and ectocervix epithelial cells and increases secretion of proton. After menopause, due to reduction in estrogen, there is alkalinization and increase in pH up to 7.0. The risk of vaginal infections, urinary tract infections (UTIs) dryness, pruritus and dyspareunia increases when pH is above 6.5. Even malignancies of cervix are associated with high vaginal pH.

ROUTE OF ADMINISTRATION

Estrogen therapy can be given in various forms like:

- Oral pills, *e.g.* esterified estrogens, conjugated equine estrogens, ethinyl estradiol, 17-beta-estradiol.
- Transdermal—patches
- Local—creams
- Vaginal—suppositories.
- The local estrogen is available as 17 beta-estradiol.
- All forms of therapy are equally equipped to help in menopausal symptom.
- However, most women use oral estrogen therapy. But the problem with this route

is the higher-dose requirement because of increased first-pass metabolism in the liver.

Estrogen in Menopausal Hormone Therapy

- Conjugated equine estrogen, 0.3 mg/0.625 mg, estradiol valerate 1/2 mg, or 17-beta oestradiol, 1 mg, are present in the most oral preparations.
- Routes—transdermal patches, sprays, gels, topical emulsion and vaginal.
- During its passage through the liver, oral estrogens increases the production of many inflammatory markers along with coagulation factors. Because of this, the risk of venous thromboembolism is increased. Also these women may have increased triglycerides and gallstones in future.
- Transdermal and local estrogen applications bypass first-pass metabolism and have the advantage of safety and accurate dosing.
- These are preferred in women intolerant to oral therapy.
- Transdermal estrogen sprays are also recently available. Once applied, these sprays reached maximum levels estradiol in serum after 18–20 hours and reached a stable concentration by 1 week of initiating their use.

Estrogen in Vaginal Form

- The United States Food and Drug Administration (US/FDA) has approved the use of low-dose vaginal estrogen in treatment of moderate-to-severe vaginal dryness and dyspareunia. These are commonly seen in women approaching menopause (genitourinary syndrome).
- Vaginal forms of estrogen HRT—cream, ring, tablet or capsule.
- These primarily act on the local tissue and help in treating the vulvovaginal dryness also.
- Minimal systemic side effects with vaginal preparations.
- Progesterone is not needed as there is no endometrial stimulation.
- Estriol cream conjugated equine estrogens (CEE) creams are available.
- Ultra-low-dose estriol 0.03 mg/day and standard dose 0.5 mg/day for 2 weeks followed by maintenance dose can be continued for a long time.
- Safety data beyond 1 year is unavailable currently.

Progesterone

- In women, who still have their uterus, progestogen is needed to prevent the increased risk of endometrial cancer when these women take oral estrogen supplementation. This unopposed action of oral estrogen makes the endometrial lining thick and increases risk of endometrial cancer if there is no cyclic withdrawal bleed.
- There are various preparations of progesterone available in the market, *e.g.* micronized progesterone, synthetic progestins, *e.g.* medroxyprogesterone acetate (MPA) or norethindrone.
- Micronized progesterone is better as it is similar to endogenously produced progesterone. It has a good absorption rate after taking orally as well as when used vaginally.
- Synthetic progestins have much better activity than natural ones (10 to 100-fold) and hence are cheaper alternative.
- Recently, combined preparations containing micronized progesterone or dydrogesterone are available.
- A woman who already has levonorgestrel-releasing intrauterine system (LNG-IUS) can be given oral or transdermal estrogens. LNG-IUS will give protection to the endometrium.

FORMULATIONS OF MENOPAUSAL HORMONE THERAPY AVAILABLE IN INDIA

Systemic Therapy

Oestrogen

- Oral CEE, 0.3 mg/0.625 mg; 17-beta-oestradiol, 1 mg/2 mg; oestradiol valerate, 1 mg/2 mg
- Transdermal oestrogen gel, 0.125 mg per 2.5 g of gel.

Progesterone

- Dydrogesterone 10 mg; micronized progesterone, 100, 200, 300, 400 mg
- Levonorgesterol intrauterine device 52 mg–release 20 µg/day

Combination of Oestrogen and Progesterone

Combined sequential—17-beta-oestradiol 1 mg and 10 mg with dydrogesterone

Continuous combined—17-beta-oestradiol and dydrogesterone 5 mg, daily.

Estrogen Therapy for Genitourinary Syndrome

Estriol cream, 0.5 mg/0.5 g of cream; oral estriol, 0.5 mg

Conjugated equine estrogen, 0.625 mg/1 g of cream.

Available Packages of Estradiol and Dydrogesterone Tablets

- Combipack of estradiol and estradiol and dydrogesterone
- Other options have estradiol (as hemihydrate) in 1 mg, 2 mg or 0.5 mg with different dosage of dydrogesterone (10 mg, 5 mg or 2.5 mg)

Estradiol (as hemihydrate) 1 mg with dydrogesterone 5 mg or 10 mg as it has progesterone component, it can be used in postmenopausal women with uterus. It helps in prevention of osteoporosis also. In this combination, estrogen is given continuously with dydrogesterone given in the last 2 weeks of the 4-week cycle **(Table 47.1)**.

Estradiol (as hemihydrate) 2 mg and dydrogesterone 10 mg, can be used in peri- and post-menopausal women with symptoms of estrogen deficiency. This can be as a result of natural menopause or after removal of ovaries. As with other similar combination, it helps in post-menopausal osteoporosis prevention. This is also given in similar fashion.

Estradiol (as hemihydrate) 0.5 mg and dydrogesterone 2.5 mg, this combination can be used as HRT. This preparation is given

Table 47.1: Important points to consider in HRT therapy

S. No.	*Points to consider in HRT therapy*
1	Before starting MHT, the symptoms can be reduced by lifestyle modifications, like reduction in weight, decreasing stress, Yoga, meditation, hypnotherapy and cognitive behavioural therapy (CBT).
2	Medications, like vitamin E, omega-3 fatty acids, isoflavones, and soya beans may be useful, as MHT comes with its own risk and contraindications and should be given only when the benefits outweigh the risk. Therefore, MHT has to be started with a very low dose and for a minimum duration.[13]
3	Vasomotor symptoms (VMS) normally appear within a couple of years from the last day of menstruation and generally continue for 5 years.
4	A lower dose than the routine dose of MHT is more effective for treating VMS[14]
5	Women who were under 52 years and presenting with peri- or post-menopuasl symptoms had associated comorbidities, like depression, anxiety, osteoporosis and insomnia[15]
6	There was a 40 to 65% improvement in symptoms with use of non-hormonal agents, like selective serotonin receptor inhibitors (SSRIs) and selective norepinephrine receptor inhibitors (SNRIs). The vasomotor symptoms improved by 50% after using gabapentin (900 mg/day) and 65% with use of pregabalin (150 mg/day)[16,17]

daily without interruption. Each packet is for 28 days.

CONTRAINDICATIONS FOR HRT[23]

- Any history or suspicion of cancer breast
- Any history or suspicion of estrogen-based cancer like uterine malignancy
- History of thrombosis or deep vein thrombosis (DVT) or pulmonary embolism (PE) or any active lesion
- Any blood clotting abnormalities, *e.g.* factor V Leiden mutation carriers
- History of thrombotic diseases of arteries, like myocardial infarction or cardiovascular illness, like stroke
- Chronic liver disease or hepatitis
- Severe headache/migraine with aura
- Any abnormal and undiagnosed bleeding from genitals
- Unknown hyperplasia of endometrium
- Protein C, protein S or antithrombin deficiency or any other thrombophilic disorders.

However, vaginal estrogen route can be used in these cases as the concentration of estrogen in blood after vaginal route is quite low.

MONITORING

Measurement of serum estradiol and progesterone is not required to test the effectiveness of therapy. Relief from menopausal symptoms and absence of adverse effects is a measure of the effectiveness of therapy and response to treatment.[23]

SIDE EFFECTS OF HRT

- Abnormal uterine bleeding
- Accumulation of fluids in third space
- Tenderness of breast
- Headaches
- Mood swings and irritability

The following symptoms need immediate stoppage of the HRT:

- Jaundice or Increase in liver enzymes
- Rise in blood pressure
- New onset of migraine-type headache
- Pregnancy.

LITERATURE REVIEW AND GUIDELINES

National Institute for Health and Care Excellence Guidelines[18]

- HRT should be discussed with menopausal and perimenopausal women suffereing with vasomotor symptoms (VMS), like hot flushes and night sweats.
- HRT should be considered in mood changes and anxiety along with cognitive behavior therapy (CBT).
- Oestrogen alone does not lead to significant increase in risk of breast cancer. Although estrogen and progesterone are associated with an increase in the risk of breast cancer, this risk reduces after HRT is stopped. HRT, if started before 60 years does not increase the risk of cardiovascular diseases.
- Refer these woman to a menopause specialist if no improvement.

International Menopause Society Guidelines[19]

- MHT is among the most effective therapy management of menopausal symptoms.
- For vasomotor symptoms, a combination of CEE and bazedoxifine (BZA) is the most effective.
- HRT can be started in menopausal women who are at risk of fracture or osteoporosis even before they reach the age of 60 or within 10 years of attaining menopause **(Table 47.2)**.

CONCLUSION

- Estrogen-containing products are widely used therapies for vasomotor symptoms and vaginal and vulvar atrophy.

Table 47.2: Different formulations—estrogen and progestins		
Oral estrogen	Conjugated equine estrogen (CEE)	0.3 mg/ 0.625 mg
	17β-estradiol	1 mg /2 mg, body-identical
Transdermal	17β-estradiol Estrogen gel	0.125 mg per 2.5 mg of gel, avoid first-pass metabolism
Oral progestrone	Norethindrone acetate	Indicated for AUB
	Micronized progesterone	100, 200, 300, 400 mg Body-identical
	Medroxyprogesterone acetate (MPA)	Strong action on the endometrium
	Dydrogestrone	10 mg
Intrauterine	Levonorgesterel	52 mg releases 20 µg/day
Combination of E and P	17-Beta estradiol + Dydrogestrone	1 mg
Continuous sequential	17-Beta estradiol + Dydrogestrone	10 mg

AUB: Abnormal urine bleeding

- They are good in preventing osteoporosis, cardiovascular disease, and dementia but they pose a serious risk of thrombo-embolism.
- HRT should be started and maintained at the lowest dose and for the shorter duration necessary to relieve the symptoms.
- Dose and duration should be tailor-made according to the patient's need and reviewed periodically.
- Risk of serious side effects is least with the low-dose regimens of HRT.
- HRT must not be used for the primary or secondary prevention of coronary artery diseases.

Transition and Menopause <1 year

1. Sequential combined regime—continuous estrogen and cyclic progesterone 12–14 days/month, (not a contraceptive)
2. Low-dose contraceptive pill, if not contraindicated.

In Women without Uterus

1. Continuous estrogen alone
2. Tibolone
3. Progesterone is added along with estrogen in hysterectomised women in cases of endometriosis, endometrial ablation and supracervical hysterectomy.

Post-menopause

1. Continuous combined—continuous estrogen continuous progesterone
2. Tibolone.

Premature Ovarian Insufficiency

1. Standard/high-dose estrogen and cyclical or continuous progesterone (not a contraceptive)
2. Oral contraceptive pill, if not contra-indicated.

Local Therapy for Genitourinary Syndrome of Menopause (GSM)

1. *For correction of deficiency:* Estriol cream 0.5 mg/day of vaginal application or tab. estriol, 1–8 mg/day, single dose before a meal OR
2. *Conjugated equine estrogen:* 0.3–1.25 mg/day of vaginal application for 15 days
3. *For maintenance therapy:* Tab. estriol 1 mg/day or estriol cream, 0.5 mg or conjugated equine estrogen, 0.3 mg—twice weekly for 2 months to 1 year.

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Chapter

48

Pelvic Congestion Syndrome

• Asmita Patil • Shraddha Mevada

Introduction

Pelvic congestion syndrome (PCS) is chronic pelvic pain in women who have varicose veins in or near the ovaries and is a common cause of chronic pelvic pain in women of reproductive age. Pelvic congestion syndrome is caused by varicosity and venous insufficiency of the ovarian veins and is usually asymptomatic. Most women with pelvic congestion syndrome are aged between 18 to 45 years and have a history of multiple pregnancies. Understanding the pathophysiology and possible causal factors will help us to give focused treatment.

ETIOLOGY

Various etiological factors have been described so far. El-Minawi[1] has classified various etiologies as follows:

a. Anatomical Causes

- Parity is one of the risk factors in the development of pelvic congestion syndrome.
- Pregnancy increases the capacity of the pelvic veins by 60%.
- Malposition of the gravid uterus, along with venous kinking, leads to venous stagnation, flow reversal, and varicosities.
- Incompetent venous valvular system under the effect of gravity results in pelvic varicosities. The resultant stasis produces congestion and pelvic pain.[2]

b. Sexual Dysfunction

Vasocongestion in the pelvic viscera may cause some pain in the female when she is sexually stimulated.

c. Hormonal Disorders

There is a higher incidence of polycystic ovaries, bulky uterus, and thickened endometrium, which all may be hormonally induced in these patients.

As the pelvic congestion syndrome is rarely known in the postmenopausal female, Taylor and Beard proposed that this condition might be related to hormonal sensitivity.[3]

d. Iatrogenic

The use of intrauterine devices and tubal ligation surgeries have been found to be associated with this condition by some studies. However, this is not proven.

PATHOPHYSIOLOGY

Anatomy of pelvic venous plexuses: It consists of various veins, like ovarian, para-ovarian, uterine, vesical, rectal, and vulvar veins. The vulvar and uterine veins, normally drain into the internal iliac vessels. The left ovarian vein drains into the left renal vein, and the

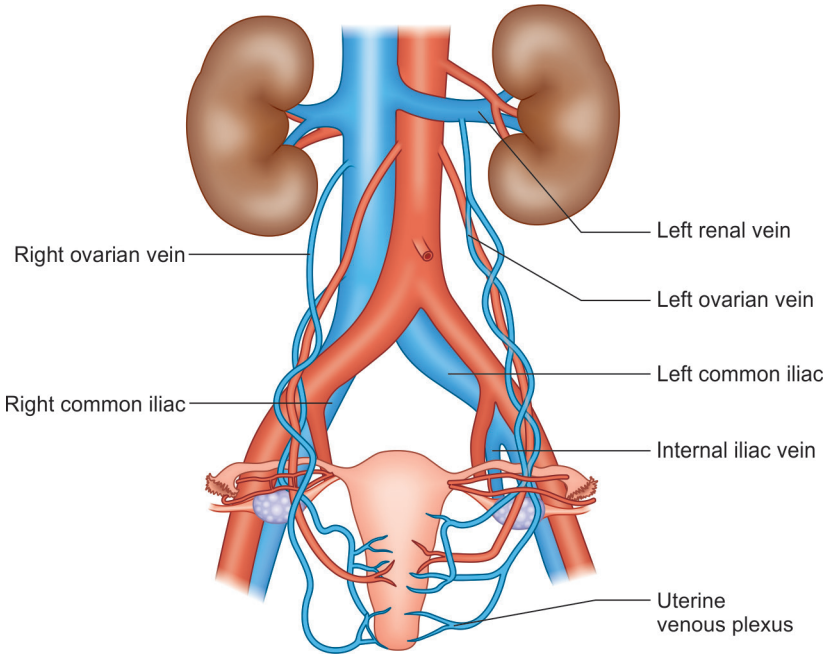

Fig. 48.1: Anatomy of pelvic venous plexuses

right ovarian vein drains into the vena cava directly **(Fig. 48.1)**.

Vascular connections between the vesical and rectal venous complexes are interlaced into each other as well as the upper thigh. These channels are relatively valveless and are gravity and vascular-tone sensitive.

a. Complete resolution of symptoms after menopause also indicates the influence of hormone levels on this syndrome. Estrogen acts as a venous dilator and can thus produce the venous dilatation which is involved in the pathophysiology of the PCS.[4]
b. In PCS, the vessels are not only enlarged but the flow through them is slowed down. Reginald[5] showed that these changes could be reversed for a short time with intravenous dihydroergotamine; by documenting pelvic venography, which offers a reduction of symptoms before and after injection.
c. Neurotransmitters produced by these abnormal vessels, like adenosine-5'-triphosphate, substance P, endothelin, and vasopressin, have been found to play a possible role.[6,7]
d. Calcitonin gene-related peptides and nitric oxide have also been implicated.[8]

SYMPTOMS

1. *Pain:* Pain is the most common symptom of PCS. It is usually intermittent and dull aching in character with intermittent aggravation by activities which cause venous stagnation, such as standing, walking, prolonged sitting, sexual intercourse, and vigorous exercises.
2. Dyspareunia and postcoital pain can also present in cases of PCS.
3. Menorrhagia and menometrorrhagia.
4. Congestive dysmenorrhea, which may mimic endometriosis.
5. Gastrointestinal symptoms, *e.g.* bloating, nausea, and abdominal pain
6. Frequency and urgency of urination can be present in some cases, which may be due to the peri-vesicle and rectal space edema due to venous congestion.

7. Headache, fatigue, and insomnia may be due to a general autonomic dysfunction.
8. Psychiatric manifestations can occur in a wide range of symptoms. Anxiety and depression are the most common.

PHYSICAL EXAMINATION

1. On per abdominal examination, tenderness is present over the bilateral iliac regions. Especially on the spine-umbilical line at the junction of the upper and middle third. At the level of the ovarian vein crossing into the bony pelvis, and on compression, it increases the venous pressure, which causes the ovarian tenderness.
2. Superficial varicosities may be present in some rare cases.
3. Vulvodynia may be present, the cervix may reveal cyanosis and an increase in cervical secretions.
4. Tenderness is present on the uterus, ovaries, posterior parametrium and the uterosacral ligaments on bimanual examination.

DIAGNOSTIC TESTS

a. A diagnostic study that can measure both the criteria of enlarged veins and reduced circulation can be used for the diagnosis of pelvic congestion syndrome. Ultrasonography, computerized tomography, magnetic resonance imaging, and radio-nuclear studies have not yet been proven to make an accurate diagnosis.
b. Laparoscopy can give a false negative impression, and chances of missing the diagnosis are there as it is usually done in the Trendelenburg position with increased intra-abdominal pressure, which leads to venous collapse. Just reverse the head down position and decrease the insufflation pressure so that an accurate diagnosis can be made.[9]
c. Pelvic venography can be the choice as a diagnostic test. It can be performed using an intravenous or transcervical (transuterine) approach. It can measure the maximum diameter of the veins and the time required for the dye to clear. The transuterine scoring system is available **(Fig. 48.2)**.[9]

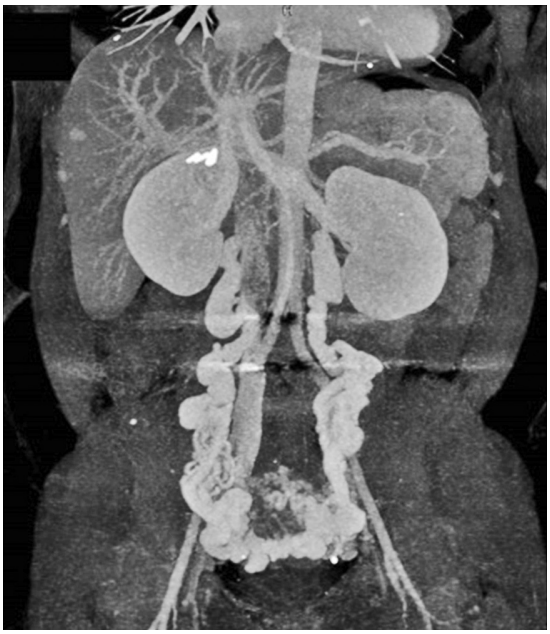

Fig. 48.2: Pelvic venogram in a patient with pelvic congestion syndrome

TREATMENT

Treatment should include elimination of the microcirculatory disorders and vascular inflammation, increased venous tone, improved lymphatic drainage and symptomatic pain relief.[10]

Psychological Approach

Neuropeptides, like substance P, neurokinin A, and neurokinin B are released in pelvic congestion syndrome.They play an integral role in the regulation of emotion pathway; they act as a modulator for pain perception and are also involved in mental stress.[11]

Psychotropic drugs, like gabapentin and amitriptyline have proven to be effective in treating chronic pelvic pain. After long-term therapy, analgesia was significantly better in

patients receiving gabapentin either alone or in combination with amitriptyline than in patients receiving amitriptyline alone.[12]

Pain Relief

Analgesics are used very commonly to reduce the pain.

Dihydroergotamine

Dihydroergotamine has systemic vasoconstrictor properties, due to which it can be used in the treatment of pelvic congestion syndrome; however, due to its narrow therapeutic margin of safety, it should be used cautiously.[13]

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are widely accepted as first-line treatment. They can be used as stop-gap therapy to offer pain relief while further investigations are performed, or more definitive treatment is found.

Suppression of Ovarian Function

Estrogen is known to cause vasodilatation. Pelvic congestion syndrome is not common after menopause, suggesting that hypoestrogenic states would result in symptom resolution.[11]

Venoactive Drugs

Venoactive drugs containing the bioflavonoids, like diosmin and hesperidin [micronized purified flavonoid fraction (MPFF)] have been studied for the treatment of PCS.[23,24]

These drugs reduce venous stasis by increasing venous tone, reduce capillary hyperpermeability and improve lymphatic drainage. MPFF has been used effectively in the treatment of symptomatic patients with PCS.[25,26]

A. MPFF

Gavrilov, et al. studied 85 women and found that MPFF, when given at 1000 mg per day for 8 weeks, and the pain was reduced by week 8 of treatment, and at 14 weeks, complete relief of symptoms was achieved and persisted for a long time with suppression in the progression of the disease. Emission computed tomography showed improvement in the pelvic circulation.

Daflon® is an oral micronized purified pleiotropic drug containing 90% diosmin and 10% hesperidin, which belongs to the flavonoid family. It improves venous tone and lymphatic drainage and reduces capillary permeability by protecting the microcirculation from inflammatory process.[27]

Mechanism of action: MPFF (daflon, 500 mg) reduces oedema by inhibiting endothelial activation. It blocks prostaglandins and thromboxane A2 which further prevents the inflammatory cascade resulting from the leukocyte-endothelium interaction delaying the reflux and inhibits the process of the vicious circle ending in raised venous pressure. Rheological disturbances also play a major role in these disorders as increased venous pressure causes leakage from the vessels and capillaries exhibiting increased vascular permeability, leading to increase in hydrostatic pressure, and overloading of the lymphatic network, leading to exudation of plasma and oedema.[28]

Venoactive drugs containing the bioflavonoids, diosmin and hesperidin have been proven effective in the medical therapy of PCS. Some research studies have shown that by improving venous tone, MPFF may restore pelvic circulation and provide relief from chronic pelvic pain and various symptoms of pelvic congestion syndrome.[29]

Side effects when taken orally—it is possibly safe for most people when used for short term. However, it can cause some side effects, such as gastritis, diarrhoea, dizziness, headache, skin redness and hives, muscle pains, altered heart rate.

Contraindicated in bleeding disorders, its safety during pregnancy and breastfeeding is not known.

Drug interactions with MPFF: When taken along with chlorzoxazone, it may increase the bioavailability of chlorzoxazone. Similar interactions are observed with diclofenac.

Drugs that are metabolised by the cytochrome P450 pathway interact with diosmin. It delays the process of metabolism of these drugs in the liver).

B. Medroxyprogesterone Acetate[14]

According to the study done by Farquhar CM, et al., medroxyprogesterone acetate (MPA) along with psychotherapy, is effective in the relief of symptoms in 60% of the patients, and only MPA has shown symptomatic improvement in 40% of the patients.[15]

Another study showed that when patients with PCS were given 30 mg MPA for 6 months, pelvic congestion was reduced, as shown by venography (17 out of 22 patients), and in 16 women, the pain relief was associated with prolonged amenorrhea. So, successful ovarian suppression is an essential constituent in the treatment of PCS.[16]

Side effects: Weight gain and bloating.

C. Depot Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate (DMPA) is a low-dose MPA that is injected at 150 mg/ml, and it has better efficacy, safety, and rapid onset of action. In a 12-month trial, DMPA depot (150 mg every 3 months) had effects equivalent to GnRH agonists.[17] However, DMPA has remarkable hypoestrogenic side effects (hot flushes, bleeding and osteoporosis).

D. Gonadotropin-releasing Hormone Agonists

Gonadotropin-releasing hormone (GnRH) agonists downregulate GnRH receptors which in turn reduces the synthesis of ovarian hormones.

A randomized controlled trial showed that when 47 patients diagnosed with PCS were treated with either goserelin acetate alone without the hormone replacement therapy or MPA for 6 months.[18] Both drugs showed significant improvements in PCS, reduced anxiety levels and better sexual satisfaction.

A side effect of GnRH analogues—symptoms of menopause, *e.g.* hot flushes, osteoporosis, etc.

E. Danazol

Danazol, a 17-ethinyl-testosterone derivative, is an anti-gonadotropic agent used for the treatment of pelvic endometriosis. It has been used as a treatment option for chronic pelvic pain associated with endometriosis. It is given a dose of 600 mg/day for endometriosis-associated chronic pelvic pain of PCS.[19] Side effects include acne, hirsutism, vaginal dryness, etc.

F. Contraceptive Implant

The synthetic etonogestrel (3-keto-desogestrel) steroid implanon.

It is a single-rod, nonbiodegradable implant. It is a progestin that is used to suppress ovarian function and steroid production, thereby producing a state of hypoestrogenism and thus helps in treatment of PCS.[20]

Implanon is a potent alternative for long-term treatment of patients with pure PCS-related pelvic pain.[21]

It has an advantage over MPA is that the patients get back their fertility by spontaneous ovulation soon after discontinuation.[22]

Effectiveness of Long-term Medical Treatment

There is insufficient literature evidence regarding the long-term usefulness of medical therapy in controlling the symptoms of PCS patients. GnRH agonists alone may be used for 6 months or a maximum of up to 2 years, along with hormone replacement therapy to avoid osteoporosis.

The limitations of using GnRH agonists for more extended periods were its menopausal side effects and costs.

Of all the options of medical treatment described above, implanon was found to

provide good results in pelvic pain relief with tolerable side effects in patients with symptomatic and pure PCS.[15,16,22]

Surgical Management of Pelvic Congestion Syndrome[30]

Patients who are resistant to medical management should be considered for surgical treatment. It includes options like stenting, ligation, embolization or sclerotherapy of the ovarian veins. Ligation of the ovarian veins can be done through a McBurney's incision or laparoscopically. In patients with a retroverted uterus and deep thrust dyspareunia, uterine suspension should be performed laparoscopically. Very rarely, hysterectomy with bilateral salpingo-oophorectomy has been done in a few cases.

A. Embolotherapy: The principle of embolization procedure is to occlude insufficient veins as close as possible to the origin of the damage by the lodgement of artificial material. In pelvic venous disorders, these vessels will be the gonadal veins, pelvic varicose veins, or sometimes tributary branches of the internal iliac veins. Embolization is typically performed on outpatient or daycare basis. This procedure is performed using metallic devices with 2% ethoxisclerol foam (sclerosing agent).

The embolization is performed 5 cm proximal to the origin of the gonadal (ovarian) veins of the left renal vein or inferior vena cava, taking care to close all the potential collateral veins in the pelvis. After embolization of the ovarian veins, internal iliac veins should be investigated, and embolization should be performed in selective cases.

B. Stenting: Venous compression syndromes may cause pelvic venous plexus hypertension and which may result in PCS. In such patients, a permanent intravascular stent is placed into the vein using a catheter to improve the venous return of compressed or occluded blood vessels. Depending on the morphology of the treated vessels and the extent of the lesions, the diameter and length of the stents can be selected, self-expandable stents are also available.

Complications can be hematoma at the procedure site, perforation of the vein, migration of the stent, and fistula formation with adjacent structures.

Complications of Surgical Management of Pelvic Congestion Syndrome

a. Persistent pelvic pain (20%) or residual pain (33%) is observed even after surgical administration of PCS.
b. There can be aesthetic damage and longer hospitalization.[30]
c. Ovarian failure is the known complication of ovarian vein ligation and oophorectomy for which hormone replacement therapy can be considered.[31]

CONCLUSION

Pelvic congestion syndrome should be kept as a diagnosis in mind in a patient with chronic pelvic pain when no visible, identifiable pathology at laparoscopy is found. Detail history or physical examination should be done in patients with chronic pelvic pain not responding to conventional therapy. Pelvic venography can be performed to confirm the diagnosis.

Medical therapy with medroxyprogesterone acetate should be tried as first line of management for at least 3 months before surgical treatment is considered. Laparoscopic venous ligation of ovarian and various pelvic veins or embolotherapy should be selected for those patients not responding to medical management.

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Chapter

49

Premature Ovarian Insufficiency

• Shaily Agarwal • Rashmi Upadhyay

Introduction

In premature ovarian insufficiency (POI) ovarian functions decrease irrevocably below 40 years of age. It can have a range of symptoms including bothersome menopausal symptoms to devastating infertility. Long-term consequences of POI can be in the form of cardiovascular disorders, cognitive decline, and osteoporosis. There is substantial evidence that these women have increased risk of mortality. Early diagnosis is necessary to prevent long-term implications as well as to minimize the effects of POI on the quality of life. Recent advances have opened new hopes for the patients seeking fertility treatment, however the success rates are not that high.

This chapter summarizes the current issues related to etiology, diagnosis as well as treatment of POI.

DEFINITION OF PREMATURE OVARIAN INSUFFICIENCY

POI means diminution of functions of ovaries well in advance the time intended for an average female. Primary amenorrhea due to ovarian defect presents as main feature of premature ovarian failure or it may present as secondary amenorrhea due to untimely diminution of ovarian follicles/arrested follicular development in less than 40 years of age.[1,2] In POI, the menopause occurs at an age more than two standard deviations below the mean age for that specific reference population. POI affects medical, psychological, and reproductive aspects of women's health.

Diagnostic criteria: Oligo/amenorrhea for at least 4 months and elevated follicle-stimulating hormone (FSH) levels >25 mIU/ml on two occasions >4 weeks apart. [European Society of Human Reproduction and Embryology (ESHRE)].

Incidence: 1 in 10,000 women by age 20; 1in 1000 women by age 30; 1 in 100 women by age 40.[3] Familial form of premature ovarian failure (POF) represents 4 to 31% of all POF cases.[4–6]

ETIOLOGY

In most cases, etiology is heterogeneous and unknown.

- Familial trait is recognized in 4 to 31% cases.[7–10]
- Mutations in more than 50 genes have been reported as etiological cause of POI, significant.[11–13]
- Forkhead Box L2 (FOXL2) mutation—POI, in the form of blephorophimosis-ptosis-epicanthus inversus syndrome (BPES) type 1.

Table 49.1: Etiology of POI

Idiopathic	Iatrogenic	• Bilateral oophorectomy, bilateral ovarian cystectomies • Chemotherapy by alkylating agents and anthracyclines • Radiation-external beam or intracavitary • Environmental toxins • Pelvic vessel embolization
Genetic	Chromosome-X defects	• Turner syndrome (45XO) or mosaic Turner (45X/46XX) • Fragile X permutation
	Syndromic defects	• Glycosylation disorders • Galactosemia • Pseudohypoparathyroidism
	Isolated defects	• Follicle-stimulating hormone receptor mutations (FSHR), (recessive) • Luteinizing hormone receptor mutations (LHR), (recessive) • FOXL2 (transcription factor involved in BPES) mutations (female-limited defect, dominant) • Bone morphogenetic protein 15 (BMP15) mutations (female-limited defect, heterozygous mutation)
Systemic defects	Infections	• Mumps oophoritis • TB • Malaria • CMV • Varicella • Shigella

- Follicle-stimulating hormone receptor (FSHR) gene mutation-primary amenorrhea and truncated follicle growth, as seen in the Finnish population.[14]
- The fragile X mental retardation gene (FMR1)-linked with POI.[15]

Ovarian surgeries constitute 64% of the iatrogenic POI cases (*i.e.* not including bilateral oophorectomy) (Table 49.1).

CLINICAL FEATURES

In POI, symptoms are highly variable; from features of hypoestrogenism, like vasomotor symptoms to symptoms reflecting signs of the underlying causative disorder. Symptoms may develop suddenly or it may develop over a longer period of time. It is also known as premature ovarian failure but the term 'primary ovarian insufficiency' more accurately represents the spectrum of ovarian dysfunction in affected women.

The most severe forms of hypergonadotropic ovarian failure present with absence of pubertal development and primary amenorrhea.[16,17] Post-pubertal onset of ovarian failure is characterized by secondary amenorrhea which may be of sudden onset or preceded by menstrual cycle changes (oligomenorrhea or polymenorrhea).[18] Female infertility is an irrevocable outcome of POF which is due to the decline in ovarian reserve.

POI patients may develop diabetes due to deficiency of endogenous estrogens which seems to have protection of functioning of pancreatic beta-cells and increases insulin sensitivity. Women with POI are prone for the development of cardiovascular disease due to endothelial dysfunction, autonomic dysfunction, abnormal lipid profile, insulin resistance and metabolic syndrome.[19] These women have shorter life expectancy as blood vessels and bones age early due to estrogen deficiency.[20–24] Alzheimer's disease,

Box 49.1: Clinical features of POI

Menstrual abnormalities

- Prolonged cycles, irregular cycles
- Primary or Secondary amenorrhea

Infertility/Subfertility

Menopausal symptoms: Vasomotor symptoms, dryness of vagina, dyspareunia, sleep disorders

Cardiovascular disease

Diabetes mellitus type 2

Autoimmune: Vitiligo, hyperpigmentation

Osteopenia/osteoporosis

Hair loss

Goiter

Fatigue

Anxiety/Depression

Alzheimer's disease

POI: Premature ovary insufficiency

hypercholesterolemia is also seen in these women. Early onset of osteopenia and osteoporosis is also common which have been attributed to the hypoestrogenism and hypoandrogenism **(Box 49.1)**.

DIAGNOSIS

4–6 months of amenorrhea under the age of 40 years with raised gonadotropins and decreased estradiol is essential to make diagnosis of POI. The hormonal levels must be checked on two occasions 4 weeks apart. FSH value >30 U/L is indicative of ovarian failure.

The investigations should aim to establish the diagnosis; once the diagnosis is made, etiology should be determined after which complications should be ruled out **(Table 49.2)**.

MANAGEMENT

Treatment should be individualized according to health issues of patient. Hormone replacement therapy (HRT) is the main stay of treatment. HRT must be continued till the normal age of menopause until contraindicated to mitigate long-term health risks.

Hormone Therapy (Table 49.3)

Menopausal Symptom

The vasomotor symptoms are due to hypoestrogenemia for which adequate systemic estrogen replacement is required. Local estrogen therapy may relieve focal symptoms. For addressing decreased libido, testosterone supplementation along with estrogen therapy may be useful but evidence about long-term safety and efficacy of androgens in menopause treatment are very few **(Tables 49.4 and 49.5)**.

For genitourinary syndrome, options available are estrogen containing vaginal creams, nonhormonal vaginal moisturizers,

Table 49.2: Investigations of POI

Lab investigations	*Tests for*	*Reason for conducting the test*
Hormonal tests	Human chorionic gonadotropins	To rule out pregnancy
	Follicle-stimulating hormone Estradiol	To evaluate HPO axis dysfunction
	Anti-mullerian hormone	To assess ovarian reserve
	Thyroid-stimulating hormone (TSH) Thyroid peroxidase (TPO) antibody 21-hydroxylase antibody	To assess thyroid function and adrenal function
Genetic studies	Karyotype Fragile X mental retardation-1 (FMR1) premutation	To rule out genetic causes
Imaging studies	Transvaginal ultrasound	To measure antral follicle count
	DEXA scan	To measure bone density

Table 49.3: Bioequivalent hormonal dosages for hormone therapy for primary ovarian insufficiency

Estrogen	*Progesterone continuous*	*Progesterone sequential*
Micronized 17-beta-estradiol (oral), 1–2 mg	Medroxyprogesterone acetate daily (oral) 2.5–5 mg	10 mg medroxyprogesterone acetate daily (oral) for 12 days
17-beta estradiol (transdermal), 100 µg	Micronized progesterone daily (oral) 100 mg	200 mg micronized progesterone daily (oral) for 12 days each month
Conjugated equine estrogen (oral), 0.625–1.25 mg		

Note: Select one of the estrogen options to be combined with one of the progesterone options.

Table 49.4: Estrogen for managing vasomotor symptoms

Oral	*Dose (mg)*
Conjugated equine estrogen	0.3, 0.45, 0.625, 0.9, 1.25 (per day)
17-beta-estradiol	0.5, 1.0, 2.0 (per day)
Ethinyl estradiol	0.005
Transdermal	
17-beta-estradiol patch	0.025, 0.05, 0.075, 0.1 (twice per week)
17-beta-estradiol gel	1.5/2 metered doses
Vaginal	
Conjugated equine estrogen	0.3125
17-beta-estradiol	0.25, 0.5, 1.0 (per day)
Transdermal spray	
Estradiol	0.53 per spray (start with 1 spray per day, adjust up to 3 sprays per day based on response)

Table 49.5: Combined estrogen/progestogen for treating vasomotor symptoms

Oral	*Dose (mg)*
Estradiol/Norethindrone acetate	0.5/0.1, 1.0/0.5 (per day)
Estradiol/Drospirenone	0.5/0.25, 1.0/0.5 (per day)
Conjugated equine estrogen/Bazedoxifene	0.45/20.0 (per day)
Estradiol/Norethindrone acetate	2.5 µg/0.5 mg (per day)
Estradiol/Norgestimate	1.0/0.09 (per day; estrogen alone for 3 days followed by estrogen/progestogen for 3 days, then repeat)
Conjugated estrogen/medroxyprogesterone	0.625/5.0 (per day; estrogen alone for days 1 to 14 then add progestogen for days 15 to 28)
Transdermal	
Estradiol/Levonorgestrel	0.45/0.015 (once per week)
Estradiol/Norethindrone acetate	0.05/0.14, 0.05/0.25 (twice per week)

Table 49.6: Treatment for genitourinary syndrome

Drugs	*Dosages*
Estradiol, 0.01%	2 to 4 g applied daily for 1–2 weeks, then 1 g applied one to three times/week (maintenance therapy)
Estradiol vaginal ring	2 mg released at 7.5 µg per day over 3 months
Ospemifene	60 mg/day oral with food
Conjugated estrogen vaginal cream	0.625 mg of conjugated equine estrogen per g; usual dosage: 0.5 to 2 g applied daily for 21 days then off for 7 days, 1–3 times/week for (maintenance therapy)
Vaginal moisturizer	10 µg applied once daily for 2 weeks, then twice weekly

and the newer oral systemic estrogen agonist–antagonist ospemifene. Ospemifene is approved by Food and Drug Administration (FDA) as a non-hormonal therapy for menopausal atrophy and dyspareunia. Ospemifene is contraindicated in women with history of breast cancer or thromboembolic disease. Creams can be applied both in intravaginal and vulvar areas. Vaginal tablets containing estradiol or the vaginal rings with low-dose estradiol provide continuous therapy for 3 months **(Table 49.6)**.

Cardiovascular Morbidity

Cardiovascular morbidity in patients with POI is due to decreased vascular endothelial function which leads to atherosclerosis, ultimately leading to decreased life expectancy **(Fig. 49.1)**

Since estrogen deficiency is the main reason for cardiovascular disease (CVD), HRT should be initiated timely in early stages to achieve optimal cardiovascular protection.[26–29]

Studies favors use of micronized natural progesterone in HRT, as it is lipid friendly, associated with reduced risk of breast cancer and effectively protects the endometrial lining of uterus.[30,31]

Furthermore, it is very essential for these women to opt for therapeutic life-style modification.

Bone Health

Estrogen has important role in bone formation and maintaining bone health. In POI, there is increased chance of osteopenia, osteoporosis and fracture which can be reduced by HRT.[32–37] Emphasis should be given to lifestyle modifications, like regular exercise, balanced diet, optimal calcium intake (1200 mg, elemental calcium) and vitamin D (1000–2000 IU/day). Avoidance of smoking is advised to optimize bone health. Bone mineral density (BMD) should be considered with patients of POI.

Since bisphosphonates have very long half-life, it should be used with caution in patients who opt for *in vitro* fertilization (IVF) by donor egg to achieve a pregnancy.[38]

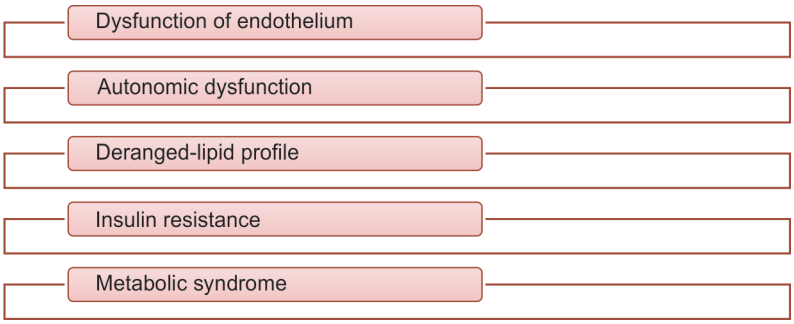

Fig. 49.1: Factors associated with cardiovascular disease

Cognition

In POI, risk of neurological dysfunction, cognitive impairment, and dementia is increased.[39–41] The cognitive decline is more rapid with earlier age of surgical POI.[42,43] It has been suggested that early initiation of HRT may have protective effects on cognitive functions.

Infertility

Despite newer approaches and treatment options in infertility management, there are limited options from these patients as they do not respond to traditional treatment options. Their options include donor egg, or donor embryo using IVF. Preconception counselling to understand the risks of chromosomal aberrations (balanced translocations or Turner mosaicism single-gene disorders-FMR1 permutation carrier state) should be offered to these patients. The risk of transmission of particular genetic mutations can be minimized by use of IVF with preconception genetic diagnosing. Oocytes, embryos, or ovarian tissue cryopreservation is a strategy that can be used to preserve fertility in selected women. It should be noted that some women having POI may spontaneously ovulate (25%), and may conceive and deliver (5–10%).[44,45] Therefore, contraception methods must be suggested to patients who do not want pregnancy.

If any young woman is planned for pelvic irradiation therapy to manage underlying disease, surgical transposition of the ovaries out of the pelvis should be offered to preserve her reproductive potential. Ovarian function suppression by gonadotropin-releasing hormone analogs is commonly employed in women anticipating chemotherapy with use of agents which can be gonadotoxic.[46]

PHARMACOKINETICS

Estrogens (Table 49.7)

Oral administration: All orally administered, naturally occurring estrogens and their esters are rapidly metabolized in the gut and the liver before reaching the general circulation through first pass effect resulting in higher estrone levels than estradiol because estradiol is metabolized by mucosa of intestine. Synthetic estrogens are degraded very slowly in the liver and other tissues leading to their high potency.

Half-life of various estrogens

- Conjugated equine estrogen (CEE): 10–25 hours
- Estradiol: 16 hours (oral) and 4–8 hours transdermaly.

The oral administration of EE, estriol and other progesterone characterized by rapid rise, up to a maximum of 1–3 hours followed by rapid decline, the level of estradiol remains elevated for up to 12 hours and decrease slowly during the following time. Important factors in the regulation of the pharmacokinetics are the conversion of estrone and the formation and hydrolysis of conjugates which are catalyzed by intestinal and liver enzymes. Interindividual variations mainly due to genetic or acquired differences in the intestinal and hepatic metabolism, while the intraindividual variations from day-to-day may be due to diet, alcohol, or drug consumption.

Non-oral administration: Estrogens are well-absorbed through the skin mucous membranes, subcutaneous fat, transdermal and topical administrations produce therapeutic plasma levels of estradiol with lower circulating levels of estrone and estrange conjugates and require smaller dose in comparison to oral route.

For women with POI, facts favor transdermal or transvaginal estradiol therapy as the first-line HRT. Compared to transdermal route, the risk of thromboembolism is more in oral routes.[47–50] This risk is more increased in obese women and in presence of clotting disorders.[49]

Progestins: In women with POI, cyclic progestin is recommended. Medroxyprogesterone

Box 49.2: Contraindications of MHT

- Undiagnosed vaginal bleeding
- History of endometrial and other hormone-dependent gynecological cancers, active cancer of breast, high risk for breast cancer
- Established CVD or increased risk of CVD
- Previous personal or family history of venous thromboembolism
- Systemic lupus erythematosus
- Severe liver disease, impaired/abnormal liver function test known or suspected pregnancy.

Box 49.3: Relative contraindications of MHT

- Hypertriglyceridemia
- Active gallbladder disease
- Obesity
- Smokers
- Migraine with aura
- Uterine fibroids, endometriosis
- Moderate risk of breast cancer

Table 49.7: Comparative effects of oral *versus* transdermal estrogens

Effect	*Oral estrogen*	*Transdermal estrogen*
Pharmacokinetics	Serum level peaks and troughs	Serum level relatively constant
Inflammatory markers (CRP)	Increased	No effect
Lipid profile	Triglycerides—increased HDL—increased LDL—decreased	Triglycerides—decreased HDL/LDL—no effect
BP	Increased	Decreased
Insulin-like growth factor-1 (ILGF-1)	Decreased	No effect
SHBG	Markedly increased	Minimally increased
Synthesis of clotting protein	Increased	No effect

Source: Good man MP. Are all estrogens equal? A review of oral vs transdermal therapy. J women health (Larchmt). 2012; 21(2):161–9.

acetate (MPA) fully induces secretory endometrium in conjunction with full replacement dose of estrogen unlike oral micronized progesterone.[51, 52]

Women who are on oral micronized progesterone, should be screened for endometrial suppression on yearly basis. There are no substantial studies showing difference in association of development of breast cancer in users of MPA and oral micronized progesterone but some studies have shown that oral micronized progesterone may be superior in improving high-density lipoprotein (HDL) levels as compared to MPA.[53]

DRUG INTERACTIONS

Majority of menopausal hormone therapy (MHT) products undergo liver metabolism mediated by the CYP450 system. Drugs like rifampicin, barbiturates increase the metabolism of MHT. Hormone therapy enhances effects of imipramine, phenytoin, carbamazepine, reduces the effects of anticoagulants, hypoglycemic agents. MHT increases the levels of thyroid-binding globulin and may increase T4 requirements.

SUMMARY

POI is associated with long-term adverse impact on woman's health. HRT is needed

for the physiological replacement of the hormones which are deficient due to decline in ovarian function. HRT also prevents cardiovascular diseases, impaired cognitive function and osteoporosis. Estrogens–progesterones are available in different forms and routes. Amongst the available options, transdermal estradiol and micronized progesterone seems to be optimal, but the treatment should be individualized.

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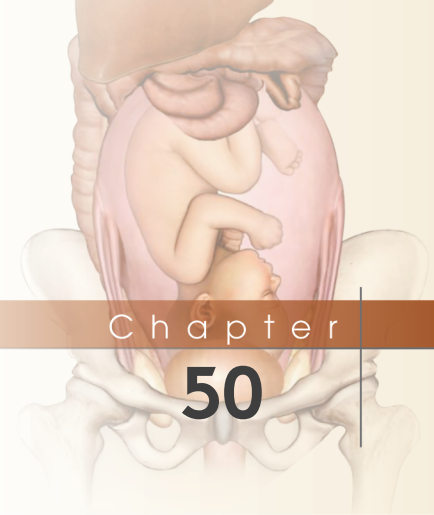


Chapter
50

Premenstrual Syndrome

• Pradnya Supe • Shailesh Kore

Introduction

Premenstrual syndrome (PMS) is defined as a condition with emotional, physical and behavioural symptoms that increase in severity during the luteal phase of the menstrual cycle, and resolve by the end of menstruation. By definition, there must be a symptom-free interval after menstruation and before ovulation.[1,2] According to American College of Obstetricians and Gynecologists (ACOG), it occurs approximately 5 days before menstruation and ends few days after menstruation starts and is accompanied by physical and psychological symptoms as PMS.[3]

Symptoms normally start 14 days before menses, causing mental instability, amongst which anger and irritability are the most prominent symptoms.[4,5] Approximately, 3–8% of menstruating women are affected by PMS, and 15–20% of women suffer from subclinical PMS.[6]

PATHOPHYSIOLOGY

The causes of PMS are multifactorial and are still unclear.[7,8]

- PMS is associated mainly with ovarian hormones. PMS is absent before puberty, during pregnancy, after menopause and during treatment with gonanotropin-releasing hormone (GnRH) analogues supports this theory.[7]
- Serotonin receptors are sensitive to estrogen and progesterone. Progesterone increases monoamine oxidase, which makes an individual susceptible to depression, while estrogen has an antidepressant effect. Therefore, low estrogen levels and high progesterone levels in luteal phase are responsible for depression.
- Allopregnanolone, which is the metabolite of progesterone, regulates the level of gamma-aminobutyric acid (GABA in the blood. GABA receptors are less susceptible to allopregnanolone, since they are exposed to high concentrations of allopregnanolone prior to the luteal phase. Low concentration of allopregnanolone in luteal phase causes anxiety, depression and aggression.
- PMS is more likely to develop in women whose mothers have had severe PMS and in monozygotic twins. PMS may have a genetic component.[8]
- BMI, exercise and diet also have a role in the pathophysiology of PMS.[9]

Symptoms

PMS is most common in women of child-bearing age; more common in women between late 20s and mid-40s. Symptoms usually start up to a week or so before the due

date of menstruation and disappear when the bleeding starts, or a few days after. Symptoms vary from month to month.

Related to Water Retention

- Abdominal bloating
- Breast tenderness
- Swelling of the extremeties
- Weight gain.

Neuropsychiatric Symptoms

- Irritability, depression, mood swings
- Forgetfulness, restlessness, tearfulness
- Increased appetite
- Anxiety, tension, confusion, headache.

Behavioural Symptoms

- Fatigue
- Dyspareunia
- Tiredness
- Loss of interest in sex, decreased libido

DIAGNOSIS

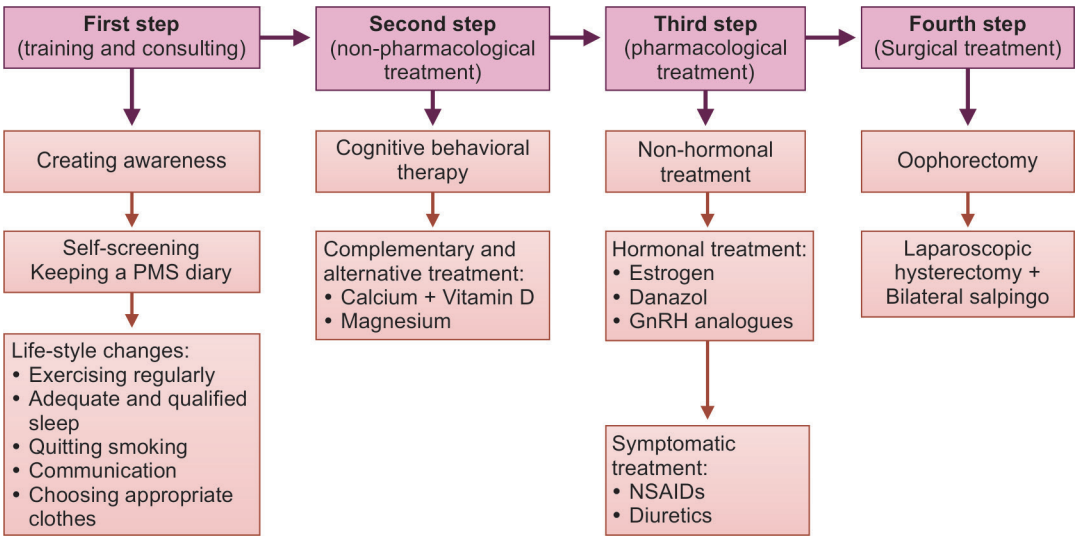
The ACOG has defined PMS as a condition in which a woman experiences at least one affective symptom and one somatic symptom that cause dysfunction in social, academic, or work performance.[3] PMS does not have a gold standard test for diagnosis.[3]

Laboratory diagnostic testing is not a must but can be used. For instance, blood count can be recommended to screen for anemia, and thyroid function to detect hypothyroidism and hyperthyroidism. Prospective questionnaires, such as the daily record of severity of problems (DRSP), calendar of premenstrual experiences (COPE) among others are the most valid and reliable tools for diagnosis of PMS. However, these methods are difficult and time consuming as patients have to notedown their symptoms daily for at least two menstrual cycles.

TREATMENT[10]

Pharmacological intervention is the best management for treatment of women with PMS **(Flowchart 50.1)**. Since premenstrual symptoms are a normal body phenomenon, treatment of PMS mainly concentrates on relief physical and psychiatric symptoms. Medications used mainly affect the hormonal activity through suppression of ovulation, while others affect neurotransmitter levels in the brain.[11] Therapy for PMS should be strictly modified based on patient tolerance.

Flowchart 50.1: Management of PMS



1. *First Step*

Raising awareness: Majority of women are unaware of PMS and do not visit a doctor for its treatment. Women in many regions do not think that PMS can be treated and they hesitate to talk to others about it.

Self screening: Educate them about changes occurring on ovaries and uterus every month to create awareness of menstrual cycle. Advice them to keep a PMS diary so that she can recognize the symptoms she has experienced and determine the type and severity of symptoms, when and how they occur.

Lifestyle changes:[12] Exercise at least 30 minutes a day. Aerobic exercises, including walking, running, cycling, and swimming elevate endorphins levels, and depressive mood is relieved.

- Adequate (at least 8 hours a day) sleep is recommended to reduce fatigue and depressive mood.
- Smoking is recommended to be stopped, because nicotine is known to worsen premenstrual symptoms.
- In case of general edema, clothing which is loose should be preferred; in case of pedal edema , comfortable and supportive shoes should be worn; and if edema is in breasts, supportive bras and elastic waist band are recommended.

Coping with stress:

Measures that can be tried also are:

- Breathing exercises,
- Relaxation exercises (meditation and yoga),
- Having a bath, adequate sleep,
- Finding and supporting a hobby,
- Massage,
- Biofeedback,
- Autohypnoses and
- Acupressure.

Diet regulation: PMS is more prevalent in women with a higher body mass index (BMI). Therefore, regulation of diet is very important.

- Six small meals at frequent intervals per day should be preferred
- Decreased fat, sugar, alcohol consumption and increased fibre, vegetables and fruit consumption are recommended
- To reduce caffeine (tea, coffee, cola) intake and salt consumption in the diet.
- Whole grain bread, barley, brown rice, beans and lentils should be included and also foods with high level of protein and complex carbohydrates.
- Iron rich food should be consumed along with sources rich in vitamin C.
- Omega-3 rich foods such as walnuts, chia seeds, flax seeds and fatty fishes should be also included in the diet.
- Calcium-rich foods, such as yoghurt and green leafy vegetables are recommended.

2. *Second Step (Non-pharmacological Treatment)*

Cognitive behavioural therapy can be useful, it helps in decreasing all symptoms and depression. It provides relaxation, management of stress and improves assertiveness.

Complementary and alternative treatments are also found to be useful.

- Commonest and most convincing of them is calcium plus vitamin D. Daily average 1000 mg calcium supplements are recommended to improve nearly all symptoms.[13,14]
- Daily 400 g magnesium intake improves premenstrual symptoms associated with depressive mood and fluid retention. The combination of magnesium + B_6 is also recommended in the management of PMS.[14]
- Other treatments, e.g. vitamin E, vitex agnus castus, saffron, ginkgo biloba, evening primrose oil, lemon grass (lemon balm), curcumin, wheat seed, isoflavones, multivitamins, refloxology and acupuncture are effective in the management of PMS, but there is insufficient evidence.[15]

3. Third Stage (Pharmacological Treatment)

A. Non-hormonal treatment: Selective serotonin receptor inhibitors (SSRI) are the first-line treatment of choice in PMS. They increase the serotonin activity in the brain.[16] They are quite effective in reducing the symptoms of PMS.

Side effects are: Nausea, insomnia, drowsiness, fatigue and decreased libido with continuous use. For reduction of side effects, SSRIs can be used intermittently. If done so, they should be started before symptoms start and should be continued throughout the luteal phase along with an antianxiety drug.[7]

B. Hormonal treatment: Hormonal therapy can improve physical symptoms by suppressing ovulation and reducing hormonal fluctuations.[7]

- ***Estrogen:*** Oral contraceptives containing drospirenone are the first choice among hormonal interventions. The use of hormone pills for 24 days and inactive pills for 4 days has improved significantly in PMS. However, estrogen alone can cause breast and endometrial tissue hyperplasia and also can cause thrombosis, so it should be given with progesterone. Since synthetic progestin causes PMS-like symptoms, it should be given in minimal doses (the dose should not exceed the maximum amount produced from corpus luteum). Alternatively, progesterone can be given directly in the form of levonorgeterol containing device.[7]
- ***Danazol:*** Low-dose danazol therapy during luteal phase is effective in reducing the sensitivity of the breasts.

  Side effects: Irreversible virilism. Also, the woman should be told about the importance of using a reliable contraceptive method as danazol can cause virilism in the fetus as well.
- ***GnRH:*** GnRH analogues are most effective in the treatment of severe PMS. However, they are not recommended for routine use. The short-term effects of these drugs are hot flashes, night sweats, insomnia and depressive mood and long-term effects are vaginal atrophy, increased cardiovascular disease and osteoporosis risk. All these are due to the hypoestrogenic environment caused by GnRH analogues. Therefore, they should not be used for longer than 6 months and if given beyond that period, bone mineral density (BMI) should be evaluated regularly.[7]

C. Symptomatic treatment

Non-steroidal anti-inflammatory drugs (NSAIDs): These have analgesic and anti-inflammatory actions that inhibit prostaglandin synthesis, which improve the symptoms of PMS. They also help in reducing cramps, headaches, back pain and sensitivity in the breasts.

- ***Diuretics:*** Diuretics help in treating the fluid retention. However, they should be carefully used with other drugs, such as NSAIDs as may cause renal injury.

D. Fourth stage (surgical treatment)

Oophorectomy: Oophorectomy treats PMS, but estrogen replacement is necessary after surgery. Along with this, progesterone treatment is needed to prevent endometrial hyperplasia.

Total hysterectomy with bilateral salphingo-oophorectomy: This may be abdominal or laparoscopic. It is successful by preventing ovulation completely. However, since this treatment method is permanent and serious, it should be preferred only if:

1. Pharmacological treatment fails,
2. Long-term use of GnRH analogues is required
3. There is an associated different gynecological condition requiring surgery.

This treatment method should be decided considering the anesthetic risks, surgical complications, infertility and the development of surgical menopause. Hormone replacement therapy (HRT) is recommended for women under 45 years of age after the surgery.

SUMMARY

PMS is a common problem and the treatment should be tailored as per age, desired fertility and the severity of patient symptoms. The treatment of PMS should be focused on improving the quality-of-life of the patient. It is important to create an awareness among the woman population regarding premenstrual syndrome.

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Chapter

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Tamoxifen in Breast Cancer

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BREAST CANCER: AN INTRODUCTION

Cancers of the breast are a category of diseases that are physiologically and molecularly diverse and that have various outcomes and treatment implications.[1]

Roughly 10% of breast cancers can be traced back to a direct ancestor.[2]

Epidemiology

International Breast Cancer Burden (Worldwide)

Breast cancer is the most frequent type of cancer in women. Every year, almost 1 in 2 persons and 1 in 11 women are diagnosed with cancer. In 2020, new cases were reported in 24.5% of the world's countries. One in four women may develop breast cancer in her lifetime **(Fig. 51.1)**.[3]

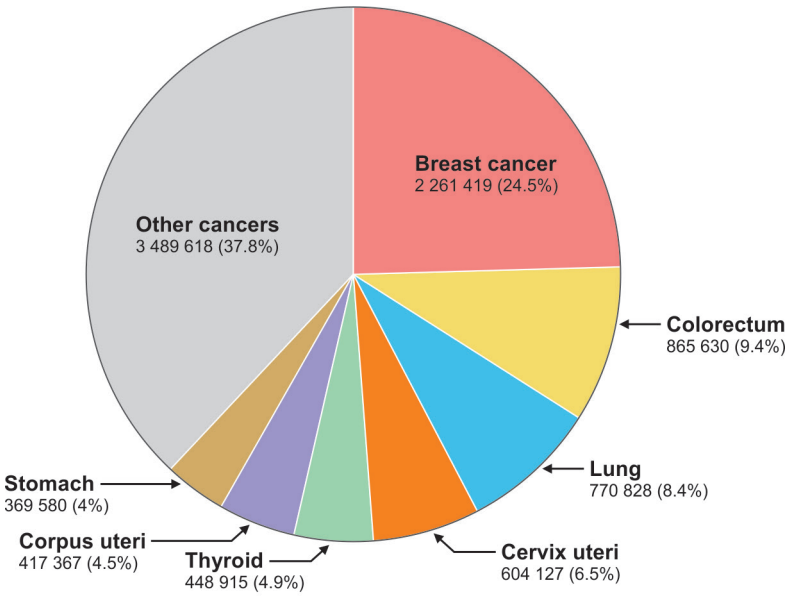


Fig. 51.1: Estimated number of new cases in 2020, worldwide, females, all ages

In India, National Breast Cancer Burden

As per the Globocan data 2020, breast cancer accounted for 13.5% (178361) of all cancer cases and 10.6% (90408) of all deaths with a cumulative risk of 2.81.[4]

RISK FACTORS ASSOCIATED WITH BREAST CANCER[5]

Non-modifiable Risk Factors

- Increasing age
- Female sex
- Menstrual factors
- Early age at menarche (onset of menses before the age of 12 years)
- Older age at menopause (onset beyond the age of 55 years)
- Nulliparity
- Family history of breast cancer
- Genetic predisposition BReast CAncer gene 1 (BRCA1) and BReast CAncer gene 2 (BRCA2) mutation carriers]
- Personal history of breast cancer
- Race, ethnicity (white women have increased risk compared with women of other races)
- History of radiation exposure.

Modifiable Risk Factors

- Reproductive factors
- Age at first live birth (full-term pregnancy after the age of 30 years)
- Parity
- Lack of breastfeeding
- Obesity
- Alcohol consumption
- Tobacco smoking
- Use of hormone replacement therapy
- Decreased physical activity
- Shift work (night shifts).

Histologic Risk Factors

- Proliferative breast disease
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia
- Lobular carcinoma *in situ*.

DIAGNOSIS OF BREAST CANCER

Until the symptoms have subsided or a benign-malignant state has been established, a detailed medical history should be taken, with special attention paid to any and all breast cancer risk factors.

Any suspicion in any one of the three tests [clinical examination, imaging (often mammography and/or ultrasonography), and needle biopsy], should prompt an open surgical biopsy to confirm a diagnosis of breast cancer.[6,7]

Important prognostic and therapeutic implications stem from the histological and molecular characteristics; hence, multiple classifications based on these features have been proposed.

Histological Classification[8–10]

Based on criteria of pathological features and invasiveness, common breast cancers can be divided into three major groups: Non-invasive (or *in situ*), invasive, and metastatic breast cancers.

Non-invasive (or In Situ) Breast Cancer

Ductal carcinoma *in situ* (DCIS).

Invasive or Infiltrating Breast Cancer

Invasive breast cancers have cancer cells that invade and spread outside of the normal breast lobules and ducts, growing into the surrounding breast stromal tissue. Together, 90–95% of all breast cancer cases fall into invasive subcategories.

- *Invasive ductal carcinoma (IDC):* IDC is the most common type of breast cancer with about 80% of all breast cancers. Most common being tubular carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, and cribriform carcinoma.
- *Invasive lobular carcinoma (ILC):* ILC is the second most common type of breast cancers and accounts for approximately 10–15% of all breast cancers.

Table 51.1: Surrogate definitions of intrinsic subtypes of breast cancer (adapted from the 2013 St Gallen Consensus)[12]

Intrinsic subtype definition	*Clinico-pathologic surrogate*	*Type of therapy*
Luminal A	Luminal A-like all of: ER and PgR positive HER2 negative Ki-67 'low' (<14%) Recurrence risk 'low' based on multi-gene-expression assay (if available)	Endocrine therapy
Luminal B	Luminal B-like (HER2 negative): ER positive HER2 negative and at least one of: Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)	Endocrine therapy for all patients, cytotoxic therapy for most
Luminal B	Luminal B-like (HER2 positive): ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	Cytotoxics + Anti-HER2 + Endocrine therapy
HER2 overexpression	HER2 positive (non-luminal): HER2 over-expressed or amplified ER and PgR absent	Cytotoxics + Anti-HER2
Basal-like	Triple negative (ductal): ER and PgR absent HER2 negative	Cytotoxics
Special histological types: A. Endocrine responsive (cribriform, tubular and mucinous) B. Endocrine non-responsive (apocrine, medullary, adenoid cystic and metaplastic		Endocrine therapy Cytotoxics

Metastatic Breast Cancers

Breast cancers that have migrated to other parts of the body are considered to be in their late stages, or stage IV. Lymph nodes under the arm are a common site for metastatic breast cancer, but other organs like the lung, liver, bone, and brain can also be affected.

Molecular Classification (Table 51.1)

Using classical immunohistochemistry (IHC) surrogate markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2) and cells proliferation regulator Ki-67 were identified which play a crucial role in molecular subtyping.[11]

Surgery, radiotherapy, chemotherapy, hormone treatment, and targeted therapies are frequently used in tandem to treat breast cancer.[12] Overexpression of ER and/or PR promotes the development of breast cancer in the vast majority of people with breast

cancer.[13,14] Tamoxifen is the most important anti-estrogen chemo drug, and has been for the past 40 years **(Figs 51.2 and 51.3)**.

TAMOXIFEN

Introduction

Initiated as an oral contraceptive, tamoxifen was later found to promote ovulation and have antiproliferative properties on estrogen-dependent breast cancer cell lines. Its synthesis occurred in 1966. V. Craig Jordan is widely regarded as the 'father of tamoxifen.' Repurposing a 'failed morning-after contraceptive' into the 'gold standard' for treating breast cancer is one of his many accomplishments.

Drug Information

As a selective oestrogen receptor modulator (SERM), tamoxifen citrate is used to treat breast cancer. Depending on the organ in question, they bind to ER and produce estrogenic or anti-estrogenic actions. In breast cancer cells and blood vessels, tamoxifen functions as a powerful oestrogen antagonist by competing with estradiol for oestrogen receptor, hence preventing estrogen-stimulated tumour growth. In the uterus, bone, liver, and pituitary, it plays a partial agonist role.[15]

Mechanism of Action

Antagonistic Action

Tamoxifen blocks estrogen's ability to promote growth of human breast cancer by competing with oestrogens (such as 17-estradiol) for binding to the ER. Competition with oestrogen for binding to ER[16] is assumed to be the mechanism through which tamoxifen exerts its anticancer actions. This means that tamoxifen can block the growth-promoting effects of autocrine and paracrine tumour growth-promoting substances, such as growth factors and angiogenic factors, by reducing the expression of estrogen-regulated genes. The end result is a slowdown in cell proliferation and a halt in the G1 phase of the cell cycle. The tumor's growth and death rates may eventually reach a new equilibrium, causing the tumour to shrink.[17]

Agonistic Action

Organs displaying agonist effects of tamoxifen include the uterine endometrium (endometrial hypertrophy, vaginal bleeding, and endometrial cancer); the coagulation system (thromboembolism); bone metabolism [increase in bone mineral density (BMD), which can slow development of osteoporosis]; and liver (tamoxifen lowers total serum cholesterol, low-density lipoprotein cholesterol, and lipoproteins **(Fig. 51.2)**.[18]

Structure

Similar to diethylstilbestrol (DES), tamoxifen has both estrogenic and antiestrogenic properties, since it is a *trans*-isomer of the triphenylethylene ring. The antiestrogenic properties of the *trans* conformations are more common than those of the *cis* ones.[18]

Pharmacodynamics and Pharmacokinetics

Absorption: Tamoxifen is readily absorbed following oral administration, with peak concentrations measurable after 3–7 hours and steady-state levels reached at 4–6 weeks.[18]

Metabolism: Several primary and secondary metabolites, including 4-hydroxytamoxifen, N-desmethyl tamoxifen, and endoxifen (4-hydroxy-N-desmethyl tamoxifen), are produced during the extensive cytochrome P450 (CYP)-mediated metabolism of tamoxifen.[21] Endoxifen, a highly effective secondary metabolite, is produced primarily via the 4-hydroxylation and N-demethylation pathways during tamoxifen metabolism. The CYP2D6-catalyzed 4-hydroxylation of tamoxifen to 4-hydroxytamoxifen accounts for only about 7% of tamoxifen metabolism, while the N-demethylation of tamoxifen to N-desmethyltamoxifen accounts for around 92%. The most major tamoxifen

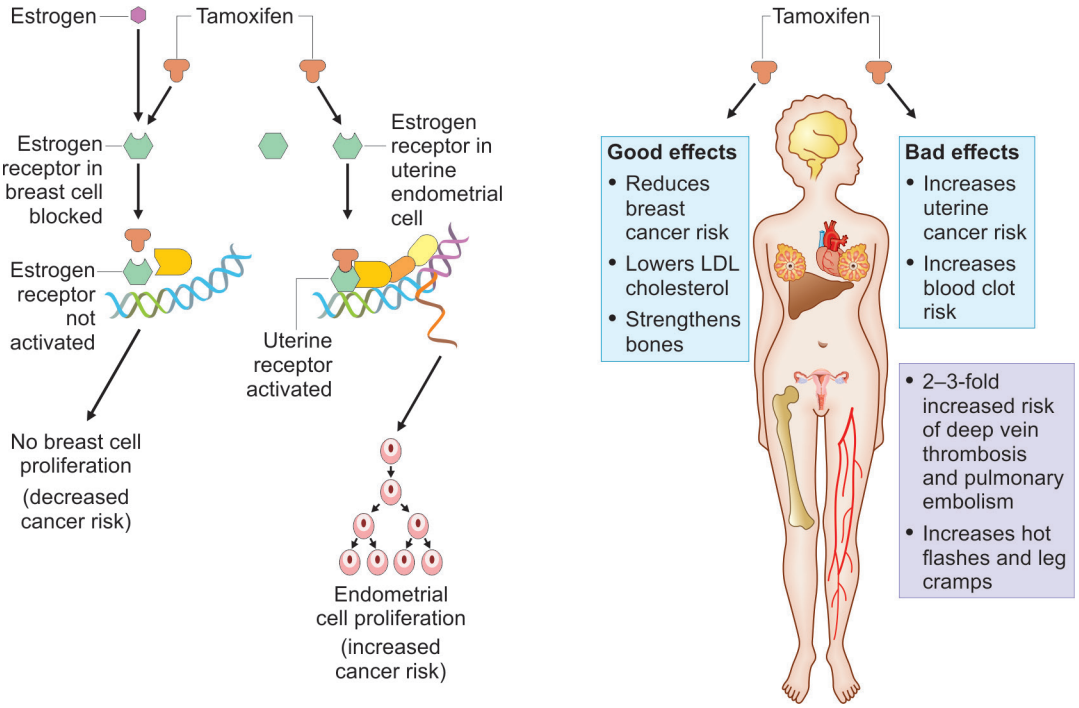


Fig. 51.2: The different mechanisms of action of tamoxifen in relation to estrogen and its receptor[19]

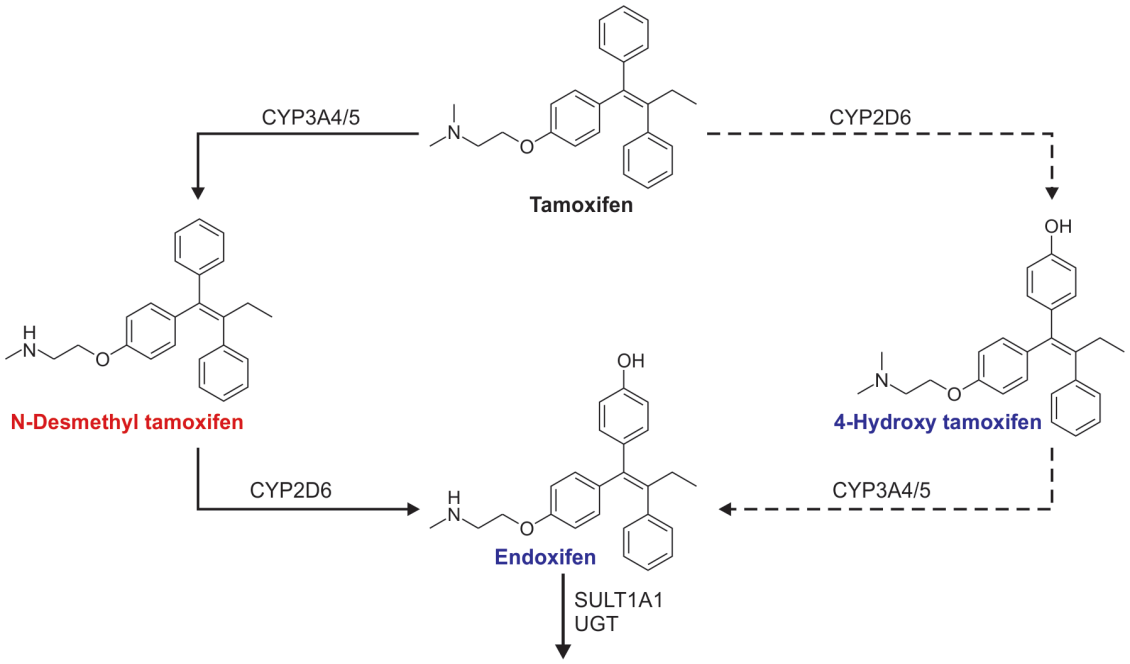


Fig. 51.3: Simplistic representation of the biotransformation of tamoxifen and its metabolites[20]. SULT: Sulfotransferase isoenzyme; UGT: UDP-glucuronosyltransferare

metabolite, endoxifen, is produced from N-desmethyltamoxifen through additional oxidation.

Even while 4-hydroxytamoxifen and endoxifen are about the same in terms of antiestrogenic efficacy, endoxifen plasma concentrations in patients taking tamoxifen therapy are, on average, about 10-fold higher than those reported with 4-hydroxytamoxifen, with considerable inter-patient variability.[22]

Biological half-life: Terminal half-life is ($t_{1/2}$) is 7 days. The elimination is biphasic, with an initial half-life of around 7 hours and a terminal half-life of 7–11 days.[18] Due to the prolonged $t_{1/2}$, 3–4 weeks of treatment are required to reach steady-state plasma levels.

Excretion: After enterohepatic circulation, glucuronides and other metabolites are excreted in the stool; excretion in the urine is minimal.

Distribution: Tamoxifen is more than 99% protein-bound in serum, predominantly to albumin.[23]

Dosage and Route of Administration

20 mg once daily, orally.[18]

Indications[18]

a. Treatment of advanced or metastatic ER(+) breast cancer in pre- and postmenopausal women.
b. Following primary excision of an ER(+) tumor as an adjuvant treatment for pre-menopausal for 5–10 years and postmenopausal women for 2–5 years to decrease the risk of cancer in the contralateral breast.
c. Breast cancer prevention in pre- and postmenopausal women with high-risk factors for 5 years.

CHEMOPREVENTION

The first medicine to successfully reduce the risk of breast cancer in otherwise healthy women was tamoxifen. Four prospective studies comparing tamoxifen to a placebo for preventing invasive breast cancer in high-risk women have been reported.

Breast cancer prevention trial [National Surgical Adjuvant Breast and Bowel Project (NSABP P-01)] was the largest trial, randomly assigning over 13,000 women with a 5-year Gail relative risk of breast cancer of 1.66% or greater, or LCIS, to receive tamoxifen or placebo. Breast cancer incidence was reduced by 49% in the tamoxifen group after a mean of 4 years of follow-up. The reduction was seen exclusively in ER-positive breast malignancies, while ER-negative tumours showed no discernible change.[18]

Three separate trials—the Italian Tamoxifen Prevention Trial[25], the International Breast Cancer Intervention Study I (IBIS-I) study, and the Royal Marsden Hospital Tamoxifen Chemoprevention Trial[24]—found that tamoxifen significantly reduced ER-positive breast cancers compared with placebo. There was no impact on mortality, but the trials did not have enough participants to reliably measure deaths from breast cancer or other causes. All four randomised trials found that tamoxifen caused similar adverse effects, such as an increased incidence of endometrial cancer, thromboembolic events, cataract development, and vasomotor abnormalities.

Women with a Gail relative risk of 1.66% or greater, those aged 35 to 59, those aged 60 and over, and those diagnosed with LCIS or atypical ductal or lobular hyperplasia are the only groups for whom tamoxifen medication is now indicated. Women who use tamoxifen also have an increased risk of developing deep vein thrombosis (DVT) (1.6 times), pulmonary embolism pulmonary embolism (PE) (three times), and endometrial cancer (EC) (2.5 times). Postmenopausal women only face an elevated risk for endometrial cancer in its first stages.

Recurrence rates in ER-positive early breast cancer are reduced by about half during treatment and about one-third in the subsequent 5 years when treated with the

selective ER modulator tamoxifen, and breast cancer mortality is reduced by almost one-third over the first 15 years when tamoxifen is used.[26] Extending tamoxifen treatment to 10 years reduces breast cancer mortality even further in years 10–14.[27,28]

Optimal Duration of Therapy

Results from the two largest studies with the longest follow-up were released, exploring the effects of tamoxifen treatment for longer than 5 years. Women who took tamoxifen for 10 years rather than 5 years experienced a 25% reduction in recurrence and a 3% reduction in mortality risk, with the advantage becoming more obvious after year 10[27], according to the adjuvant tamoxifen: Longer against shorter (ATLAS) experiment. The results of the aTTom (adjuvant Tamoxifen—To offer more?) experiment, in which patients were randomly allocated to receive tamoxifen for either 5 or 10 years, corroborated these findings. Breast cancer recurrence and mortality rates were both reduced in those who received treatment for longer.[28] These data prompted the American Society for Clinical Oncology (ASCO) to revise its recommendations for using endocrine therapy as part of adjuvant treatment. It is suggested that women take tamoxifen for a period of 5 years if they are premenopausal or perimenopausal. If the patient is still premenopausal after 5 years of treatment with tamoxifen, she should be offered a further 5 years of treatment **(Flowchart 51.1** and **Table 51.2)**.

Contraindications

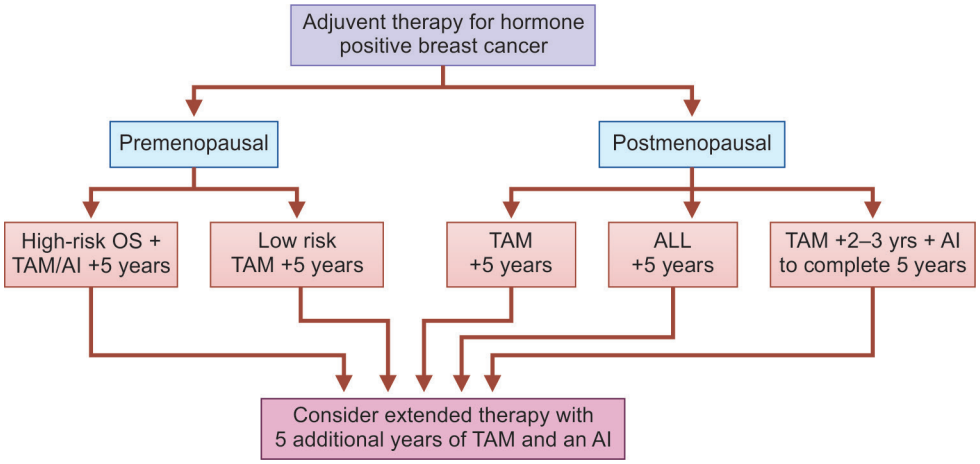
- Pregnancy
- Lactation
- History of DVT or PE
- Hypersensitivity to tamoxifen.

Drug Interactions

Anti-depressants

Recent research has found no evidence for a clinically relevant effect of using antidepressants that suppress CYP2D6 activity, like selective serotonin reuptake inhibitors (SSRIs), on tamoxifen's activity against breast cancer. Due to their low potency as CYP2D6 inhibitors, the antidepressants venlafaxine and desvenlafaxine are not contraindicated here. However, caution should be exercised when mixing SSRIs with CYP-metabolized medicines. It is important to use caution while dosing SSRIs like escitalopram and citalopram in the elderly due to a decrease in CYP2C19 metabolism that occurs with age.

Flowchart 51.1: Algorithm for choice of endocrine therapy in the adjuvant setting



OS: Ovarian suppression; Tam: Tamoxifen; AI: Aromatase inhibitor (letrozole, anastrozole, exemestane)[30]

Rifampicin

Strong CYP3A4 inducers should not be used with tamoxifen. Strong CYP3A4 inducers (*e.g.* rifampin) reduce tamoxifen efficacy.[31]

Adverse Effects

Tamoxifen is extremely well-tolerated by most patients with breast cancer. In early trials of tamoxifen for adjuvant therapy, fewer than 5% of patients withdrew from therapy because of toxicity.

- Menopausal symptoms
- Hot flashes
- Atrophic vaginitis
- Irregular menses
- Ocular toxicity
- Thromboembolic events
- Thrombocytopenia or leukopenia
- Endometrial cancer (low grade) endometrial hyperplasia and polyps.

Menopausal Symptoms

Menopausal symptoms are the most common side effect of tamoxifen, and they occur more frequently in premenopausal women than in postmenopausal women. Up to 80% of people on tamoxifen report experiencing hot flashes throughout treatment **(Fig. 51.4)**.[31]

Table 51.2: Tamoxifen therapy in adjuvant setting; benefits and adverse effects and their management[29]

Therapeutic agent	*Benefit*	*Adverse effects*		
Tamoxifen		*Type*	*Prevalence*	*Management*
	When used for 5–10 years in the adjuvant setting, is associated with a 9.2% ± 1%, absolute reduction in breast cancer mortality over 15 years			
		Hot flashes	40–80%	• Lifestyle changes in dressing, bedding • For severe symptoms try SSRI, SNRI (venlafaxine, citalopram, escitalopram, sertraline) • Avoid paroxetine, fluoxetine
		Venous thromboembolism (VTE)	Relative increase in VTE by a factor of 2–3 Pulmonary embolism: 0.2% over 5 years	• Use caution in patients with factor V Leiden hetero or homozygosity, recent fracture, recent surgery, immobilization, prior history of VTE • Treat VTE per guidelines
		Endometrial cancer	Relative increase by a factor of 2.7 (1.2/1000 patient-years)	• No routine surveillance for standard-risk patients • Premenopausal patients: Any irregular vaginal bleeding to be investigated with endometrial biopsy • Postmenopausal patients: All vaginal bleeding to be investigated with endometrial biopsy; otherwise, only normal routine gynecologic exam per standard guidelines.
		Ocular pathologies	Cataract: 3.7% of patients	• Consider yearly eye examination
		Fatty liver disease	Up to 33% of patients	• No routine screening recommended • If fatty liver documented, obtain liver enzymes every 3–6 months • Stop tamoxifen if liver enzymes exceed twice the upper limit of normal

Venous Thromboembolism

In older women, tamoxifen increases the incidence of venous thromboembolism by a factor of two to three.[32,33] Extending therapy in the adjuvant situation from 5 to 10 years appears to increase the risk. Surgery, fracture, immobilisation, and heterozygous factor V Leiden carrier status, all increase the likelihood of complications. For women younger than 54 years of age, however, extending tamoxifen use to 10 years (0.2%) does not appear to raise the risk of fatal pulmonary embolism.[32,34] Therefore, individuals undergoing surgery must abstain from taking tamoxifen for 4 weeks before to the procedure.[35]

Endometrial Cancer

Although the absolute annual risk of endometrial cancer remains low at 1.2 per 1000 patient-years, tamoxifen has been linked to a risk that is enhanced by a factor of 2.7 for both endometrial cancer and uterine sarcoma. While taking tamoxifen, a patient has an increased risk of cancer, which gradually decreases once treatment is stopped.[37]

Guidelines for monitoring uterine cancer in tamoxifen users are as follows:[36]

- A hysteroscopy or endometrial biopsy (or both) should be performed on premenopausal women who experience abnormal bleeding. Women past menopause who experience unexpected vaginal bleeding, should follow the same advice.
- Routine age-appropriate screening is advised for postmenopausal women without vaginal bleeding.

Ocular Pathologies

An increased risk of cataracts (3.7%), corneal pigmentation (reversible), and retinal deposits (irreversible) in combination with macular edoema and vision loss (38%) have all been linked to tamoxifen exposure. Although these problems are less common, it is nevertheless suggested that everyone get an annual eye examination.[38]

Fatty Liver Disease

Overall, tamoxifen has a favourable effect on lipid profile.[39] However, it was recently discovered that one-third of tamoxifen patients develop fatty liver as a side effect, as detected by ultrasonography. Because steatohepatitis rarely has serious consequences, frequent screening is unnecessary. You can keep taking tamoxifen unless your liver enzymes are twice as high as normal. Liver function tests should be performed on patients with diagnosed fatty liver disease every 3–6 months.[29]

BENEFITS OF TAMOXIFEN[31]

- Slows development of osteoporosis in postmenopausal women.
- Lowers total serum cholesterol, low density lipoprotein cholesterol and lipoprotein and raises A-I levels, potentially decreasing the risk of myocardial infarction.

TAMOXIFEN AND CHEMOTHERAPY

According to the results of the Southwest Oncology Group Intergroup Trial S8814 (INT-0100), tamoxifen is currently administered sequentially after chemotherapy rather than concurrently. In this trial, 1,477 postmenopausal women who tested positive for receptors and lymph nodes were randomly assigned to receive either tamoxifen monotherapy, tamoxifen plus cyclophosphamide, doxorubicin and fluorouracil (CAF), or CAF followed by tamoxifen. Eight-year disease-free survival (DFS) estimates were 67% for sequential CAF followed by tamoxifen and 62% for concurrent CAF + tamoxifen ($p = 0.045$), demonstrating somewhat lower DFS and OS (overall survival) for the concurrent arm.[40]

TAMOXIFEN RESISTANCE

De novo or acquired resistance may occur after treatment, limiting the effectiveness of tamoxifen in many patients.

Types of Tamoxifen Resistance

a. Loss of ER (ER isoform) expression and ER gene alterations, such as deletion and point mutation, are hallmarks of *de novo* (at the onset of treatment) disease. Patients with cytochrome P4502D6 (CYP2D6) deficiency are resistant to tamoxifen because they lack the enzyme necessary to convert the drug into its active metabolite, endoxifen.
b. Resistance to endocrine therapy was acquired by nearly all metastatic patients following treatment.

Although ER is present in many tumours, some of them become hormone-independent on their own, and some tumours that are originally ER-positive, eventually become ER-negative. At least 66% of tamoxifen resistant tumours retain ER expression, and many of these tumours shrink in response to second-line hormone therapy.[41]

Patients with ER-positive breast cancer, and notably those with metastatic disease, typically benefit most from endocrine therapy. There is evidence that some breast tumours, despite expressing ER, are more resistant to endocrine therapy than others. Molecular profiling studies performed over the past decade have provided evidence for this theory by allowing the classification of ER-positive tumours into the luminal A and luminal B subtypes. While luminal A is more placid and endocrine-responsive, luminal B is more aggressive and endocrine-resistant **(Fig. 51.4)**.[41]

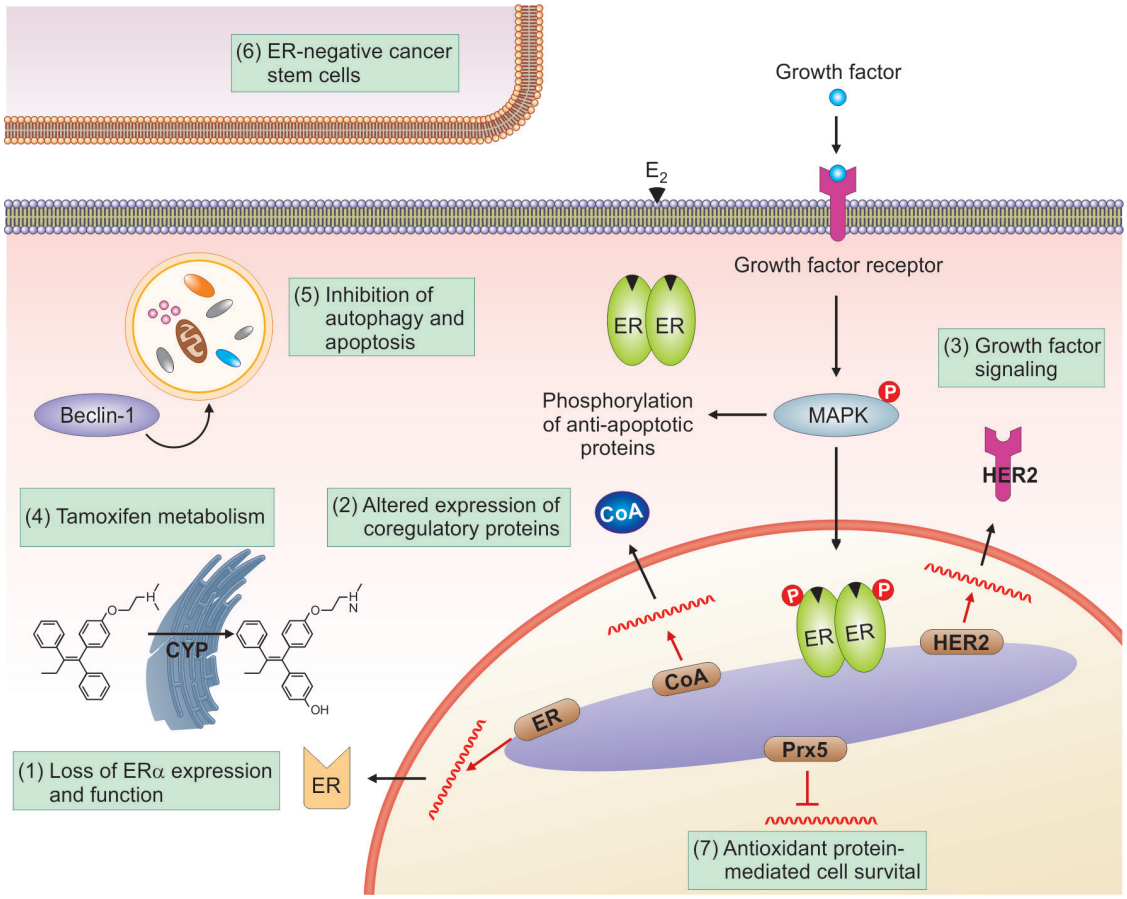


Fig. 51.4: Scheme showing the different mechanisms of tamoxifen resistance[42]

Causes of Tamoxifen Resistance[42]

1. Loss of ER expression and function lead to disappearance of the molecular target for tamoxifen
2. Altered expression of coactivators or coregulators that plays a critical role in ER-mediated gene transcription
3. Ligand-independent growth factor signaling cascades that activate kinases and ER-phosphorylation
4. Altered availability of active tamoxifen metabolites regulated by drug-metabolizing enzymes, such as CYP2D6
5. Regulation of autophagy and/or apoptosis
6. ER-negative cancer stem cells that differentiate over growth inhibition of ER-positive cancer cells upon antiestrogen treatment, and
7. Antioxidant protein-mediated cell survival in which tamoxifen prevents repression of antioxidant proteins, such as Prx5 leading to cell survival and resistance to tamoxifen treatment.

TRIALS

- The NSABP has finished a second chemoprevention trial comparing the effectiveness of tamoxifen and raloxifene in reducing the risk of breast cancer in women at high risk of developing the disease after menopause. In this follow-up prevention trial, raloxifene, another selective oestrogen receptor modulator, was chosen for the experimental arm due to evidence suggesting that it may be even more effective at reducing breast cancer risk than tamoxifen, without causing the same side effects on the uterus.
- During the P-2 study, also known as the study of tamoxifen and raloxifene (STAR trial), 19,747 postmenopausal women with an increased risk of developing breast cancer were randomly assigned to receive either tamoxifen or raloxifene. Both drugs were found to be effective in reducing breast cancer risk in the initial report from the P-2 study, but raloxifene was linked to fewer side effects. New research shows that raloxifene is just as effective as tamoxifen in preventing invasive breast cancer, with less side effects. Long-term tamoxifen use was associated with a considerably increased chance of developing endometrial cancer.[43]
- *Aromatase inhibitors trial:* Aromatase inhibitors dramatically lower oestrogen concentrations, blocking the activation of ER-positive breast cancer cells, but only in postmenopausal women. Recurrence rates are decreased more by aromatase inhibitors when taken for 5 years compared to when taken for 5 years following 2–3 years of tamoxifen.[44]

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Chapter

52

Tibolone as Postmenopausal Hormonal Therapy

• Seema Mehrotra • Pooja Mishra

Introduction

Menopause is a natural biological process that occurs in women, typically between the ages of 45 and 55 years. This hormonal change can lead to various physical and psychological symptoms that can impact a woman's quality-of-life.

Some of the symptoms associated with menopause include:

- *Musculoskeletal pain:* Fluctuations in hormone levels, especially estrogen, can lead to joint and muscle discomfort in some women.
- *Insomnia:* Changes in hormone levels and hot flushes can disrupt sleep patterns, leading to insomnia or difficulty in falling and staying asleep.
- *Forgetfulness:* Some women may experience cognitive changes, such as forgetfulness or difficulty with memory during menopause.
- *Hot flushes:* Hot flushes or night sweats are common symptoms of menopause, caused by hormonal fluctuations.
- *Sexual dysfunction:* Decreased estrogen levels can lead to changes in vaginal tissues, reduced lubrication, and decreased sexual desire in some women.
- *Osteoporosis:* After menopause, the decline in estrogen levels can result in bone loss and increase the risk of osteoporosis, a condition characterized by weakened bones that are more prone to fractures.

TIBOLONE

Tibolone is a synthetic steroid that has been used in hormone replacement therapy (HRT) for menopausal women. It has a unique pharmacological profile due to its conversion into three active metabolites: 3α-hydroxytibolone, 3β-hydroxytibolone, and Δ4-isomer. Each of these metabolites has specific effects on different tissues and organs, contributing to tibolone's therapeutic actions.

The 3α-hydroxytibolone and 3β-hydroxytibolone metabolites provide estrogenic effects in tissues like the vagina, brain, and bone, while having minimal effects on the endometrium. This is beneficial because it reduces the risk of endometrial proliferation and associated issues, like vaginal bleeding. These metabolites also interact with estrogen receptors, leading to improved bone mineral density and reduced bone turnover, like traditional hormone replacement therapy.

Tibolone's effects on the breast are unique. The hydroxymetabolites inhibit the action of sulfatase, which reduces the conversion of estrone to estradiol, resulting in lower estrogenic stimulation. The Δ4-isomer has

progestagenic and androgenic properties, binding to progesterone and androgen receptors. The progestational activity helps reduce endometrial proliferation, which means that additional progestins are not required for therapy. The androgenic effects can affect sex hormone-binding globulin levels and lead to increased levels of unbound testosterone.

In hepatic tissue, the Δ4-isomer affects lipid levels, reducing high-density lipoproteins (HDL) and triglycerides, while leaving low-density lipoproteins (LDL) relatively unchanged.

Pharmacokinetics

Absorption and distribution: Tibolone is rapidly and extensively absorbed after oral administration. However, due to extensive metabolism, the plasma concentrations of the parent compound (tibolone itself) remain very low. Instead, plasma concentrations of the metabolites (3α-OH-tibolone, 3β-OH-tibolone, and delta-4-isomer of tibolone) are higher and appear within 30 minutes, peaking around 1–1.5 hours after administration. Food does not significantly affect the extent of absorption.

Metabolism: Tibolone undergoes metabolism through multiple pathways in the GI tract and liver. The metabolites include estrogenic (3α-OH-tibolone and 3β-OH-tibolone) and progestogenic/androgenic (Δ-4-isomer) compounds. The activity of tibolone on different tissues depends on the activity of the enzyme sulfatase, which converts tibolone to its active metabolites. Tibolone differs from estrogens in that sulfatase activity is inhibited in breast tissue, resulting in reduced estradiol formation in the breast.

Elimination: The elimination half-life of the 3α- and 3β-hydroxymetabolites is approximately 6–8 hours. The parent compound (tibolone) and the Δ4-isomer do not reach appreciable plasma levels, making it difficult to determine their elimination half-lives. Tibolone is mainly eliminated in the form of sulfated metabolites through the feces, with some excretion via the urine. Renal function does not significantly affect the elimination of tibolone.

Effects of tibolone on various tissues: Effects on bone—tibolone stimulates estrogen receptors in bones, leading to decreased osteoclast activity and restoration of the balance between bone resorption and formation. This therapy is commonly used for the prevention and treatment of osteoporosis. Unlike traditional HRT, which requires continuous use for osteoporosis protection, tibolone has shown positive effects on bone density even after withdrawal.

Effects on the breast: Tibolone exhibits effects on breast tissue that differ from those of estrogen. Its metabolites inhibit enzymes involved in converting estrone sulfate to estradiol, leading to reduced estrogenic activity in breast tissue. Observational studies suggest that tibolone may have a lower incidence of breast tenderness and pain compared to traditional HRT. While some studies have indicated a potential increased risk of breast cancer with estrogen-containing HRT, data on tibolone's impact on breast cancer risk are still inconclusive and require further investigation.

Effects on cardiovascular parameters: Historically, HRT was believed to provide cardiovascular protection in postmenopausal women, but recent studies have raised doubts about its benefits. Tibolone affects various parameters related to cardiovascular health. It has been shown to reduce triglyceride, total cholesterol, and lipoprotein levels, but it may transiently lower high-density lipoprotein cholesterol (HDL-C). Tibolone also impacts the fibrinolytic system, potentially explaining its lack of association with venous thromboembolic events. However, its long-term effects on cardiovascular outcomes require further research.

Thromboembolic events: Clinical trials have not demonstrated an increased risk of venous thromboembolic events with tibolone use. Tibolone may be discontinued temporarily before elective surgery that involves prolonged immobilization.

Additional considerations: Tibolone is not recommended for patients with liver disease or a history of hepatotoxicity. Vaginal bleeding or spotting may occur in some women during the initial months of therapy. Monitoring of fluid retention and cardiovascular parameters is essential in patients who may be prone to changes in fluid status. Tibolone does not have significant drug interactions and is not dependent on renal function for dosage adjustments. Routine physical examinations, including family medical history, blood pressure checks, and pelvic examinations, are recommended during tibolone therapy.

The women's health initiative (WHI) trial results suggest that HRT, including tibolone, should be prescribed at the lowest effective dose and for the shortest duration necessary to address menopausal symptoms while balancing potential risks.

Dose: Oral formulation in tablet form.

Tibella: 2.5 mg, daily.

Oral: Swallow the tablet whole with water/fluid irrespective of meal, daily at same time.

If doses are missed may be taken as soon as they are remembered within 12 hours of the usual time. If ≥12 hours have elapsed, the missed dose should be skipped and the next dose taken at the usual time.

Clinical uses: Tibolone is prescribed for short-term treatment of vasomotor symptoms associated with menopause in postmenopausal women. It may offer advantages over traditional HRT in certain aspects, but further studies are needed to fully understand its long-term effects on various tissues and disease outcomes. Here are some of the main uses and benefits of tibolone:

- *Menopausal symptom relief:* Tibolone is effective in alleviating menopausal symptoms, such as hot flashes, night sweats, vaginal dryness, and mood swings. By activating estrogen receptors, it helps restore hormonal balance in menopausal women, reducing discomfort and improving their overall quality-of-life.
- *Bone health:* During menopause, women are at an increased risk of osteoporosis due to declining estrogen levels. Tibolone can help prevent bone loss and reduce the risk of fractures by enhancing bone density and strength.
- *Vaginal health:* As estrogen levels decrease, vaginal tissues may become thinner and drier, leading to discomfort and pain during intercourse. Tibolone's estrogenic effects help restore vaginal health by promoting vaginal lubrication and increasing the thickness of the vaginal lining.
- *Cardiovascular protection:* Estrogen has a protective effect on the cardiovascular system by maintaining healthy blood vessels and regulating cholesterol levels. Tibolone's estrogenic activity can provide cardiovascular benefits for postmenopausal women, reducing the risk of heart disease and stroke.
- *Mood enhancement:* Menopausal women often experience mood swings and emotional disturbances due to hormonal fluctuations. Tibolone's effects on neurotransmitter systems, including serotonin and dopamine, may help stabilize mood and improve emotional well-being.
- *Libido improvement:* Tibolone's androgenic properties can boost sexual desire in some women by stimulating the androgen receptors responsible for sexual function.
- *Prevention of endometrial hyperplasia:* Tibolone's progestogenic activity can help protect the endometrial lining of the uterus from excessive growth, reducing the risk of endometrial hyperplasia and potential cancer.

- Tibolone is not intended for contraceptive use and should only be administered to patients with an intact uterus.

Adverse Reactions

While tibolone is generally well-tolerated by most women, like any medication, it can cause adverse reactions in some individuals. The severity and occurrence of these side effects can vary from person to person. Some of the potential adverse reactions of tibolone may include:

- *Breast discomfort:* Some women may experience breast tenderness or enlargement while taking tibolone.
- *Vaginal bleeding:* Irregular vaginal bleeding or spotting may occur, especially during the first few months of tibolone treatment. This may be a reason to seek medical advice to ensure there are no underlying issues.
- *Headaches:* Headaches can be a side effect of tibolone use, although they are usually mild and temporary.
- *Gastrointestinal disturbances:* Tibolone may cause gastrointestinal symptoms, such as nausea, abdominal pain, bloating, or indigestion.
- *Weight changes:* Some individuals may experience weight fluctuations while on tibolone therapy.
- *Mood changes:* While tibolone can improve mood in some women, it may cause mood swings or changes in others. In some cases, it can lead to depressive symptoms.
- *Skin reactions:* Rarely, tibolone can cause skin reactions, such as rash or itching.
- *Hair changes:* Some women may experience changes in hair growth patterns or hair loss.
- *Cholelithiasis:* There is a small increased risk of developing gallstones (cholelithiasis) while taking tibolone.
- *Fluid retention:* Tibolone may cause mild fluid retention in some individuals.
- *Allergic reactions:* In rare cases, tibolone can trigger allergic reactions, which may manifest as hives, swelling, difficulty breathing, or severe skin reactions.

It is crucial to note that the list above is not exhaustive, and other side effects may occur. Additionally, some women may not experience any adverse reactions while taking tibolone.

Contraindications

1. *Hormone-sensitive cancers:* Such as breast cancer or endometrial cancer. Since tibolone has estrogenic effects, it could potentially stimulate the growth of hormone-sensitive tumors.
2. Undiagnosed vaginal bleeding
3. Previous blood clotting disorders
4. Hypersensitivity to tibolone
5. Pregnancy and breastfeeding
6. Porphyria.

It is crucial to inform your healthcare provider about your complete medical history, including any underlying health conditions or medications you are taking, before starting tibolone or any other hormone replacement therapy.

Dosage Forms Specific Issues

Tibolone may contain lactose and should not be used in individuals with galactose intolerance, congenital lactase deficiency, or glucose-galactose malabsorption syndromes.

Other Warnings/Precautions

- Tibolone should be administered only to patients with an intact uterus. It should not be used for combined hormone therapy, and a separate progestogen should not be added to tibolone therapy. The treatment should be reserved for symptoms affecting the quality-of-life.
- The risks *vs* benefits of tibolone therapy should be carefully considered. Tibolone treatment should continue only as long as the benefits outweigh the risks.
- In surgery patients, tibolone therapy should be interrupted 4 to 6 weeks before

elective surgery involving prolonged immobilization and restarted only when the patient is fully mobile.

Monitoring Parameters

Regular monitoring is recommended for patients on tibolone therapy. Monitoring parameters include:

- Physical examination, family medical history, and blood pressure
- Breast and pelvic examinations, including a Papanicolaou smear
- Mammography, blood serum glucose, serum calcium, triglycerides, and cholesterol levels
- Liver function tests (LFTs)
- Signs and symptoms of thromboembolic disorders
- Glycemic control in patients with diabetes
- Lipid profiles in patients with hyperlipidemias
- Thyroid function in patients on thyroid hormone replacement therapy.

It is essential for healthcare providers to be aware of these contraindications, warnings, and precautions while prescribing Tibolone and to monitor patients regularly to ensure their safety and well-being during treatment.

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Chapter
53

Treatment of Abnormal Uterine Bleeding

• Ruchika Garg • Rajshree Katke

Introduction

Abnormal uterine bleeding (AUB) describes any disturbance in volume, regularity, frequency, or duration of menstrual flow. This terminology was standardized by the International Federation of Gynecology and Obstetrics (FIGO) in 2009 and replaced the previously used 'dysfunctional uterine bleeding (DUB).' AUB includes the subgroups of heavy menstrual bleeding (HMB), intermenstrual bleeding (IMB), and prolonged menstrual bleeding.[3] HMB has replaced the term 'menorrhagia' and is defined as excessive menstrual blood loss, which interferes with a woman's physical, social, emotional, and/or material quality-of-life and which can occur alone or in combination with symptoms.[4] IMB has replaced the term 'metrorrhagia' and refers to any bleeding that occurs between clearly defined and predictable menstrual cycles (*i.e.* typically every 21 to 35 days).[5] The term acute AUB describes an episode of bleeding that, in a clinician's opinion, is of sufficient quantity to require immediate intervention to prevent further blood loss. Chronic AUB refers to abnormality in menstruation over the majority of the past 6 months.[3]

The evaluation and management of AUB will be most effective when the most likely etiology of bleeding is considered. The PALM-COEIN classification proposed by the Menstrual Disorders Working Group of FIGO in 2011, allows for the standardization of terminology for clinicians. Etiologies of AUB are classified as being either related or unrelated to uterine. The etiologies unrelated to structural abnormalities are further subdivided into categories following the acronym COEIN: Coagulation disorders, ovulatory disorders, endometrial disorders, iatrogenic causes, and not otherwise classified causes. This classification is now widely accepted in obstetrics and gynecology. Abnormalities—the acronym PALM: Polyps. Adenomyosis, Leiomyoma, and evaluation of acute AUB should begin with a rapid assessment of the patient's clinical status, especially hemodynamic stability and volume status. Orthostatic vital signs can be helpful to further evaluate a patient's volume status, even when she is asymptomatic and vitally stable at rest. Some patients may present with an acute worsening of chronic HMB, or after a prolonged bleed, and so manifest acute symptoms of hypovolemia or anemia. Young, otherwise healthy patients with acute AUB and those with chronic AUB may compensate for the blood loss and therefore may not manifest symptoms or aberrations in vital signs at the time of presentation. Continued bleeding in this

setting can lead to acute decompensation requiring rapid resuscitation. Patients with hemodynamic instability should be resuscitated as any trauma patient would be. Two large bore IVs, canulas should be placed, even if the patient does not require immediate resuscitation given the impending risk of acute decompensation. Resuscitation should begin with isotonic fluids, with transition to cross-matched blood when available. It is not necessary to await laboratory results to begin blood transfusion in the setting of hemodynamic instability. O-negative blood can be used in the absence of a type and screen. Vital signs should be monitored frequently during and after resuscitation efforts. If the patient has not stabilized after three units of blood, especially if she is becoming increasingly unstable, massive transfusion protocol should be started in accordance with hospital operating procedure to ensure replacement of clotting factors and platelets as well as blood. Extensive research has been done to best quantify how much menstrual blood loss a patient is experiencing. Previously, quantitative measurements were used and HMB was defined as more than 80 ml per cycle.

Subjective pictorial blood loss charts have not correlated well with actual blood lose and also do not account for the impact AUB has on a patient's life. Instead, the focus should be on the frequency, regularity, duration, and volume of bleeding, as well as how this impacts the patient's lifestyle.[6] A patient should be asked if cycles are frequent, normal, infrequent, or absent, with either regular or irregular intervals, if the duration of bleeding is prolonged, normal, or shortened, and if the flow is heavy, normal, or light.[5] In regard to HMB, common questions include the number of menstrual products used on the heaviest day, size and number of blood clots, and the need for simultaneous use of menstrual products.[6] Anecdotes patients who report soaking one or more menstrual pads or tampons per hour an at increased risk for acute decompensation and need for resuscitation, questions about timing of bleeding should include whether the IMB or postcoital bleeding. Eliciting associated symptoms of pain with endocrinologic or other symptoms may suggest systemic etiology. Elicit a detailed family history, ask about systemic conditions, infections, medications and coagulation.

Pelvic examinations should be performed in a private room with a chaperone present. Ensure that all supplies are present prior to beginning including a stretcher with stirrups, along with gloves, a speculum, adequate lighting, and several large and small cotton swabs. Whereas bleeding that does not pool or is not actively coming out of the os on or is dark red is likely non-acute. Visualization of the cervix can optionally be technically difficult, if there are many or large fibroids distorting the orientation of the uterus. In these situations, it may be more helpful to begin with a bimanual examination to evaluate the orientation, size, and regularity of the cervix uterus and then proceed to speculum examination.

LABORATORY AND DIAGNOSTIC TESTING

Do urine pregnancy test upon presentation and all patients presenting with AUB should have a complete blood count (CBC) performed to evaluate for anemia. The CBC should be evaluated in conjunction with a patient's clinical picture and not be used alone to dictate management, specifically need for transfusion. A patient with acute AUB may have a normal hemoglobin, if her body has not yet equilibrated, and similarly a patient with chronic AUB may not report any symptoms but be severely anemic. In the acute setting, a blood type and cross should be ordered in case the patient requires transfusion. Pelvic ultrasound, including transvaginal and transabdominal approach, as the first-line imaging modality. But diagnosing genital pathology, pelvic ultrasound, specifically

transvaginal sonography (TVS) is usually the best way to evaluate the endometrial lining. Structure abnormalities, such as submucosal leiomyoma and endometrial polyps may also be visualized on TVS; however, saline infusion sonohysterogram (SIS) is ultimately superior for this evaluation. Computed tomography (CT) is indicated when malignancy or non gynecologic etiology are suspected. Magnetic resonance imaging (MRI) can better delineate uterine leiomyomata, but are typically not required for acute or first-line diagnosis.

ACUTE MANAGEMENT

Ultimately, management of AUB must account for multiple factors including the patient's age, reproductive life goals, medical history, and ability to access health care. In the acute setting, the patient's hemodynamic stability and severity of bleed guide immediate management. Any further management of AUB should be tailored to the most suspected etiology whenever possible. First-line treatment for acute AUB is medical management. However, there is limited data on the success rates of various regimens. Two small studies of women treated with high-dose progestin for acute AUB found high rates of rapid decrease in bleeding and 76% to 100% cessation of bleeding within 3 to 5 days. High-dose progestin was administered as oral medroxyprogesterone acetate (provera) 20 mg, TID, for 3 to 7 days +/− 20 mg daily for 21 days or as intramuscular depot medroxyprogesterone acetate (DMPA) 150 mg once.[8,9] Acute AUB can also be controlled with high-dose oral estrogen, which is as effective as high-dose progestin, when provided as a combined oral contraceptive (COC), TID for 7 days followed by daily for 21 days.[8] For patients with contraindications to estrogen use, like pre-existing cardiovascular risk factors or known or suspected malignancy, high-dose progestin is first-line therapy. High-dose intravenous estrogen has little data to support its efficacy and is not recommended because of the higher risk for venous thromboembolism (VTE) and cost associated with its use. Intravenous or oral tranexamic acid can also be used as an adjuvant to hormonal therapies to slow or stop acute AUB. A study of trauma patients showed a statistically significant reduction in death from bleeding and all cause mortality with the early use of tranexamic acid.[10] Moreover, there was no significant increase in vascular occlusive events. Studies in cases of postpartum hemorrhage have also shown that early administration of tranexamic acid reduces blood loss, bleeding-related mortality, and requirements for blood transfusion.

In concert with medical treatment, if AUB is very severe, hemostasis can be attempted with mechanical tamponade to temporize bleeding and allow sufficient time for medications and blood transfusion to achieve their full benefit. The vagina can be packed with long continuous sterile gauze. This is especially useful if bleeding is deemed to be vaginal or cervical in nature. If brisk uterine bleeding is suspected, balloon tamponade may be more beneficial. Depending on the estimated size of the uterus, a Foley catheter, rectal balloon, or Bakri balloon can be placed within the uterus, ensuring the balloon is proximal to the internal os and inflated to 40 to 60 ml in size. It is important to note that distension of the vagina with sterile gauze packing can kink the ureter causing urinary retention. It is advised that Foley catheter be placed in the bladder prior to placement of vaginal packing or balloon tamponade. Moreover, precise urine output is helpful in judging a patient's volume status and adequacy of resuscitation efforts. If a patient can be stabilized and bleeding temporized, uterine artery embolization (UAE) by interventional radiology may be considered.

Several studies have illustrated the successful use of levonorgestrel-releasing intrauterine system (LNG-IUS) in treating the ultrasound imaging bleeding symptoms of adenomyosis.[24–28] A randominzed controlled

trial (RCT) comparing LNG-IUD showed equivalent outcomes for bleeding at short-term follow-up the minor superiority of LNG-IUS in some aspects of quality-of-life. Long-term use showed satisfaction rates of 72% with the levonorgestrel-intrauterine disease (LNG-IUD) with symptomatic decrease in uterine volume, and the option for future fertility. Other hormonal contraceptive methods may also be effective in decreasing adenomyosis-mediated HMB and dysmenorrhea. Hysterectomy remains the definitive treatment to patients who no longer desire fertility.

Uterine fibroids are benign smooth muscle tumors. Their growth is dependent on endogenous estrogen and progesterone, although they also contain aromatase allow for endogenous production of estrogen to stimulate their own growth. Fibroids are very common, occurring in up to 80% of women by age 50.[30] They occur most often during the reproductive years, when estrogen and progesterone levels are highest, and usually decrease in size following menopause. Nearly, 50% of patients with fibroids are asymptomatic: However, fibroids can cause significant symptoms. Symptoms are characterized as bleeding symptoms or bulk symptoms. Bleeding symptoms most commonly are HMB and prolonged menstrual bleeding and are attributed to increased endometrial surface, increased uterine vasculature, and changes in uterine contractility, as well as possible abnormalities in endometrial angiogenesis and hemostasis. Bulk symptoms accur when the uterine size and shape is distorted by fibroids causing compression of the ureters, bowel, bladder, or other surrounding structures, leading to urinary retention or incontinence, bowel dysfunction, dyspareunia, back pain and even hydronephrosis. Fibroids may be diagnosed on pelvic exam, on pelvic ultrasound, or incidentally on abdominal/pelvic imaging for a different indication. Ultrasonography is the preferred initial imaging modality for fibroids given its high sensitivity.[30] Fibroids can be classified as pedunculated, subserosal, myometrial and submucosal.

Leiomyomas

In asymptomatic patients, expectant management is encouraged. In patients who are pregnant at the time of diagnosis, it is important to counsel them regarding the possibility of myomal degeneration and pain as the pregnancy progresses and the growing uterus requires increased blood flow to support the growing fetus. Anticipatory guidance can also be provided regarding the possible symptomatology of uterine fibroids so that a patient may follow-up for gynecologic care if she becomes symptomatic and desires treatment in the future.

Medical management allows for the improvement of symptoms without the risks of surgery and allows for fertility preservation. The adverse side effects of some medications limit their use, and patients may outgrow the therapeutic effects of medical treatment eventually requiring surgical management. Non-hormonal medical treatments include non-steroidal anti-inflammatory drugs (NSAIDS) and tranexamic acid. NSAID can improve dysmenorrhea and HMB associated with fibroids by blocking prostaglandin synthesis.

A 2013 Cochrane review found a 30% decrease in menstrual bleeding with NSAID use compared to placebo. Tranexamic acid is also helpful to decrease HMB associated with fibroids. Additionally, tranexamic acid is thought to lead to possible reduction in fibroid size via ischemia. This may cause increased pain as well.[38] Some medical treatments work by blocking the stimulatory effects of fibroid growth and size and/or to decrease HMB, but are not consistently useful in stopping or decreasing fibroid size gonadotropin-releasing hormone (GnRH) agonists work at the level of the hypothalamus to suppress the hypothalamic–pituitary–ovarian (HPO). In the first 3 to 6 months of treatment,

women may have improvement and a 30 to 50% reduction in fibroid volume primarily because of their mechanism of action, GnRH agonists cause decreased bone mineralization from hypoestrogenism reason, their use is limited to 6 months without hormone add-hack therapy. GnRH agonist administration prior to hysterectomy or myomectomy led to a significant reduction in uterine volume, fibroid volume, duration of stay, and pre- and postoperative hemoglobin levels. GnRH agonists are given prior to hysteroscopic myomectomy, resulting in decreased operative times absorption, and ease of procedure.

Surgical management of fibroids in patients who desire future fertility is myomectomy and runs the risk of fibroid recurrence. Myomectomy can be performed hysteroscopically in the case of submucous fibroids, vaginally prolapsing fibroids, or abdominally for large or numerous fibroids. Laparoscopy myomectomy can also be performed, although minilaparotomy, morcellation in an endocatch bag or posterior colpotomy may be required to remove fibroids from the peritoneal cavity safely. Definitive surgical management for fibroids is via hysterectomy. It is recommended that the least invasive approach of hysterectomy be performed to minimize recovery time, blood loss, and complications.

Patients who desire uterine preservation but do not desire future fertility can pursue a UAE performed by interventional radiologists. UAE causes devascularization and involution of fibroids. It has been compared to both myomectomy and hysterectomy and found to result in less postoperative pain and faster recovery but with increased minor complications and hospital readmissions. Although, UAE has been shown to have a reoperation rate ranging from 20 to 33% for persistent or new fibroids, it can be a safe option for the patient who is not a good surgical candidate.

Malignancy

AUB may be the first presenting symptom of several different gynecologic malignancies. Discussion of gynecologic malignancies in the pediatric and adolescent population is beyond the scope of this chapter, however, bleeding may be the presenting symptom for young patients with vaginal or cervical sarcomas or malignant germ cell or sex cord-stromal ovarian tumors.[51] The reproductive-aged and older patient may present with postcoital bleeding, IMB, or postmenopausal bleeding. Cervical cancer and cervical intraepithelial neoplasia (CIN) anecdotally are most associated with postcoital bleeding. One study found that 11% of women with cervical cancer presented with postcoital bleeding. Cervical cancer is the fourth most common cancer diagnosed in women. About two-thirds of cervical can cer cases are squamous cell carcinoma and are associated with exposure to human papillomavirus (HPV), whereas the remaining one-third are adenocarcinoma.

Postcoital bleeding can also be caused by surface vaginal lesions from vaginal intraepithelial neoplasia (VAIN) or vaginal cancer.[53] Primary vaginal cancer is rare, but the majority of cases are squamous cell carcinoma and caused by HPV.[51] A thorough examination of the vagina and cervix can help to determine the source of bleeding in the case of macroscopic lesions. It is important to note that macroscopic lesions can cause torrential bleeding following sexual intercourse to the highly vascularized tumor.

Women with persistent postcoital bleeding may benefit from colposcopy to allow for thorough evaluation of the vagina and cervix.[54] Endometrial cancer is the fourth most common gynecologic cancer, and its instance is steadily increasing. Type-1 endometrial cancer is endometrioid adeno-carcinoma, which is estrogen-dependent. It is estimated that nearly 50% of type-1 uterine cancer are secondary to obesity alone.[55] Type-2 endometrial cancers are either

clear cell or serous carcinoma of the uterus and are much less common. Endometrial cancer, especially type 1 most commonly present with AUB, including HMB, IMB, or postmenopausal bleeding. Endometrial biopsy should be performed as a first-line evaluation for any patient above the age of 45 who presents with AUB to evaluate for endometrial intraepithelial neoplasia (EIN, previously endometrial hypertrophy) or anyone below the age of 45 with prolonged estrogen exposure, such as morbid obesity or anovulatory cycles from polycystic ovarian syndrome (POS).[3] Ultrasound imaging for evaluation of endometrial thickness is helpful in the postmenopausal patient when trying to differentiate uterine atrophy from hyperplasia as the cause for bleeding. In the case of EIN or a patient's desire for fertility-sparing management, high-dose oral progestins and the ING-IUD have been used to avoid or postpone surgery.

AUB-M is used for patients with AUB that are diagnosed with malignancy or premalignancy (CIN, VAIN, EIN). These lesions should still be classified according to the appropriate WHO or FIGO system.

Coagulopathies

It is estimated that up to 13% of women with HMB have some variant of Willebrand's disease, and up to 20% of women may have an underlying coagulation disorder.[58] Platelet dysfunction has been reported in approximately 50% of women with unexplained HMB.[59,60] It is important to screen for underlying disorders of hemostasis. If a patient's screen is positive, laboratory testing should be ordered including CBC with platelets, prothrombin time (PT) and partial thromboplastin time (PTT).

Von Willebrand's disease results from either a decreased quantity or quality of von Willebrand factor (vWF) resulting most commonly in increased mucocutaneous bleeding. The condition usually presents at the time of menarche when anovulatory cycles are more common and vWF is at its nadir.[61] If von Willebrand's disease is suspected, additional laboratory testing should include vWF ristocetin cofactor activity, vWF antigen, and factor VIII.[60] Inherited or Acquired platelet disorders include abnormalities of platelet aggregation and adhesion, platelet secretion, and signal transduction. Alone, inherited bleeding disorders most commonly lead to prolonged menstrual bleeding and HMB, but can also worsen symptoms caused by structural etiologies of AUB (PALM). Unlike with other etiologies of AUB, non-steroidal anti-inflammatory diseases (NSAIDs) should be avoided with abnormal uterine bleeding related to coagulopathy (AUB-C) given their irreversible effects on platelets: However, cyclo-oxygenase-2 (COX-2) inhibitors may be used.[63] Tranexamic acid is commonly used in bleeding disorders and has been shown to have utilized for patients with blood loss.

Desmopressin (DDAVP) is used to increase plasma factor VIII and the release of endogenous VWF to improve hemostasis.

Surgical interventions in patients with AUB-C can prevent further blood loss: However, they are associated with a higher risk of postoperative hemorrhage, including delayed bleeding up to 10 days of surgery. Patients require an adequate bleeding risk assessment and plan for hemostatic coverage. Given the risk of hemorrhage with hysterectomy, patients with HMB from AUB-C can benefit from less invasive options such as endometrial ablation. Second generation endometrial ablation techniques, which do not rely on hysteroscopy, have been shown to be safer than first-generation techniques because of less risk of blood loss. Major procedures in patients with high risk of bleeding will require clotting factor replacement. It is also important to note that these patients should have factor levels monitored for up to 10 days post-operatively.

Ovulatory

Regular, monthly cycles result from ovulatory function, which produces ovarian steroids and corpus luteum to release progesterone. Exposure of the endometrium initially to estrogen alone causes endometrial proliferation, followed by exposure to estrogen and progesterone which causes secretory changes, and then withdrawal of both hormones as the corpus luteum involutes and results in shedding of the lining. Ovulatory dysfunction generally causes irregular bleeding and HMB because of the effects of unopposed estrogen on the endometrium. Ovulatory dysfunction can be physiologic, such as during adolescence, perimenopause, or lactation or it can be pathologic, caused by aberrations at any level in the HPA axis can also be caused by other endocrine disorders that affect the HPO axis, such as thyroid disorders and hyperprolactinemia. In adolescents, the HPO axis is immature and does not have the hormonal feedback necessary for ovulation. This resolves in 60 to 80% of adolescents within 3 years of menarche. In perimenopause, the ovaries are producing estrogen, and there are fewer follicles to release an egg and develop into a corpus luteum, leading to anovulatory cycles. Hypothalamic hypogonadotropic amenorrhoea caused by stress or malnutrition blunts the pattern of GnRH-releasing hormone from the hypothalamus, thus disrupting the HPO axis preventing ovulation.

Polycystic ovary syndrome (PCOS) is the most common cause of ovulatory dysfunction-associated AUB (AUB-O) in reproductive-aged women. According to the Rotterdam criteria, the diagnosis of PCOS is made when patient has two of the following findings: Oligomenorrhea, hyperandrogenism, and cystic ovaries on ultrasound. It is unclear what causes PCOS: it is likely several etiologies can lead to the clinical syndrome. However, the condition is chronic anovulation. It is often associated with insulin resistance and obesity leading to increased levels of estrogen from peripheral conversion. Several studies have shown a return to ovulatory cycles with sustained weight reduction in patient with PCOS. Because of chronic anovulation, it is very important to evaluate EIN and endometrial malignancy in these patients.

Endometrial ablation is not recommended given the need for accurate endometrial surveillance in the context of increased risk for uterine pathology with tamoxifen use.[91, 92] Hysterectomy may be performed if fertility is not desired and AUB symptoms are not manageable.

COCs are typically contraindicated in patients with a history of ischemic cardiac or neurologic event or venous thrombosis or pulmonary embolism. Thus, treatment for AUB in this population typically relies on progestin-only-based methods. LNG-IUS is the superior method to treat AUB in these patients. DMPA can also be used, and studies have shown that there is no significantly increased risk of patients developing a hematoma at the injection site of DMPA.[95] If surgical intervention is required, endometrial ablation has been shown to have high satisfaction rates in patients taking anticoagulants.[96,97] Finally, hysterectomy by the least invasive method may be performed.

Classified for those pathologies that are rare, are poorly defined, or do not fit. These diagnoses include uterine arteriovenous malformations (AVM), endometrial pseudo-aneurysms, myometrial cesarean scar defects, and chronic endometritis.

The appropriate treatment for both endometrial hypertrophy and cesarean scar defects requires additional study, but studies have shown hysteroscopic repair, laparoscopic repair, or vaginal repair to have success rates of 59%, 86%, and 89%, respectively. Lastly, chronic endometritis that is noninfectious in etiology is sometimes seen in DMPA or IUD users. AUB resulting from endometritis because of DMPA or IUD use is considered iatrogenic, whereas idiopathic chronic endometritis in nonusers is categorized as

AUB-N. Chronic endometritis is generally successfully treated with a 2-week course of doxycycline after which AUB symptoms should improve.

Conclusion

AUB is a common complaint among patients presenting for gynecologic care. Using updated terminology for the description of AUB enables clinicians to more accurately describe patient complaints and determine their impact on quality-of-life. The PALM-COEIN classification facilitates the correct diagnosis and management of AUB based on most likely etiology. Most cases of AUB, even in acute situations or when etiology is uncertain, can be managed effectively with available, safe medical regimens. The evaluation of AUB can be initiated at the patient's first presentation and need not preclude short-term management. Depending on the etiology, long-term management may require surgery or consultation with the interdisciplinary healthcare teams.

HORMONE THERAPY

Estrogens

Effective in controlling acute, profuse bleeding. Exerts a vasospastic action on capillary bleeding by affecting the level of fibrinogen, factor IV, and factor X in blood, as well as platelet aggregation and capillary permeability. Estrogen also induces formation of progesterone receptors, making subsequent treatment with progestins more effective.

Most AUB is secondary to anovulation. In these patients, endometrium continues to proliferate with asynchronous development. As blood supply is outgrown, irregular shedding occurs. Bleeding might be controlled acutely with high-dose estrogen for a short period of time. Several hours are required to induce mitotic activity, so most regimens require 48 hours of therapy before continued bleeding is ruled a treatment failure.

Conjugated Equine Estrogen (Premarin)

Women in perimenopause generally are estrogen deficient and might experience bouts of estrogen withdrawal bleeding. Many of these patients will recover regular menses and develop an improved sense of well-being with the initiation of hormonal replacement therapy, including estrogen and a progestin.

Side effects: Abdominal pain, back pain, breast enlargement, breast tenderness, headache, arthralgia pharyngitis, sinusitis, diarrhea.

Progestins

Progestins inhibit estrogen-receptor replenishment and activate 17-hydroxysteroid dehydrogenase in endometrial cells, converting estradiol to the less active estrone. Medroxyprogesterone acetate (provera) is the most commonly used progestin in this country, but other types, including norethindrone acetate and norethindrone (micronor), are equally efficacious. In some patients in which systemic progestins are intolerable due to side effects, a progestin-secreting IUD (mirena) may be considered.

Synthetic progestins have an antimitotic effect, allowing the endometrium to become atrophic if administered continuously. These drugs are very effective in cases of endometrial hyperplasia. In patients with chronic eugonadal anovulation who do not desire pregnancy, treatment with a progestin for 10–12 days/month will allow for controlled, predictable menses and will protect the patient against the development of endometrial hyperplasia.

Progestin Therapy

- Most commonly used hormonal therapy given during luteal phase.
- Norethisterone is the most commonly used oral progestogen in the treatment of AUB

Progestins modulate the effect of estrogen on target cells and metabolism of estrogen, the endometrium is maintained in a state of antimitosis and antigrowth.

Medroxyprogesterone Acetate (Provera)

Short-acting synthetic progestin. Drug of choice for patients with anovulatory AUB. After acute bleeding episode is controlled, can be used alone in patients with adequate amounts of endogenous estrogen to cause endometrial growth. Progestin therapy in adolescents produces regular cyclic withdrawal bleeding until positive feedback system matures.

Stops endometrial cell proliferation, allowing organized sloughing of cells after withdrawal. Typically, does not stop acute bleeding episode but produces a normal bleeding episode following withdrawal.

Provera only indicated for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer, 5 or 10 mg, PO for 5–10 days; begin day 16 or 21 of the menstrual cycle. Progestin withdrawal bleeding usually occurs within 3–7 days after discontinuing medroxyprogesterone.

Combination Oral Contraceptives

Contraceptive pills containing estrogen and progestin have been advocated for women with AUB who desire contraception. Apparently takes longer to induce endometrial proliferation when progestin is present. In long-term management of AUB, COCs are very effective. Ethinyl estradiol and a progestin derivative (ovral, lo-ovral, ortho-novum, ovcon, genora, orthocyclen, and others) reduce secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from pituitary by decreasing amount of GnRH.

Oral Contraceptive

- Action is probably mediated through endometrial atrophy. Oral contraceptive pills (OCPs) suppress pituitary gonadotropin release, thus inhibiting ovulation.
- High doses of estrogen are associated with an increased risk of thromboembolism.
- These should be avoided in women with thrombosis or a family history of idiopathic venous thromboembolism.
- The most common side-effects include weight gain, abdominal discomfort, and mid-cycle breakthrough bleeding.

Not suitable in patients desiring pregnancy, adverse effects are edema, weakness, amenorrhea, breakthrough bleeding, change in menstrual flow, spotting, anorexia, deep vein thrombosis (DVT), thrombophlebitis, depression, dizziness, abdominal pain, change in weight, cholestatic jaundice.

Androgens

Certain androgenic preparations have been used historically to treat mild to moderate bleeding, particularly in ovulatory patients with AUB. Use of androgens might stimulate erythropoiesis and clotting efficiency. Androgens alter endometrial tissue so that it becomes inactive and atrophic.

Danazol (isoxazole derivative of 12-alpha-ethinyl testosterone), 200 mg daily for 3–4 cycles is recommended.

Side Effects

Acne, hirsutism, weight gain, reduced high density lipoprotein.

Nonsteroidal Anti-inflammatory Drugs

Blocks formation of prostacyclin, an antagonist of thromboxane, which is a substance that accelerates platelet aggregation and initiates coagulation. Prostacyclin is produced in increased amounts in menorrhagic endometrium. Because NSAIDs inhibit blood prostacyclin formation, they might effectively decrease uterine blood flow. NSAIDs have been shown to treat menorrhagia in ovulatory cycle.

- NSAIDs reduce blood loss by 25–30%, but not all women respond similarly.
- Commonly used are mefenamic acid and naproxen but are less effective than tranexamic acid.

- NSAIDs have shown only minimal effect in anovulatory menorrhagia.
- Side-effects include minor gastrointestinal disturbance, headaches and enervation may occur.

Tranexamic Acid

- Reduces blood loss by 50%
- However, many women remain menorrhagic and many are non-compliant due to daily dosing
- Large doses of tranexamic acid are required
- Incidence of GI side-effects, intermenstrual bleeding are relatively high
- Risk of thrombogenic disorders is a concern.

GnRH Agonists

Work by reducing concentration of GnRH receptors in the pituitary via receptor down regulation and induction of postreceptor effects, which suppress gonadotropin release. After an initial gonadotropin release associated with rising estradiol levels, gonadotropin levels fall to castrate levels, with resultant hypogonadism. This form of medical castration is very effective in inducing amenorrhea, thus breaking ongoing cycle of abnormal bleeding in many anovulatory patients. Because prolonged therapy with this form of medical castration is associated with osteoporosis and other postmenopausal side effects, its use is often limited in duration and add-back therapy with a form of low-dose hormonal replacement is given.

Indications of GnRH Agonist

- Utility should really for short-term use.
- Particularly useful in the treatment of leiomyoma, which can reduce considerably in size when ovarian hormone levels are suppressed.
- May be used prior to surgical intervention in women with fibroids, or for those in whom surgery is not suitable or desirable
- Studies have demonstrated excellent efficacy, with an amenorrhea rate of up to 90% with GnRH agonist use.
- Danazol is not frequently used because of its androgenic and long-term lipid profile side-effects.

Depot leuprolide acetate (lupron) suppresses ovarian steroidogenesis by decreasing LH and FSH levels.

Injection-site reactions include abscess, emotional lability, acne/seborrhea vaginitis, vaginal bleeding or discharge, rash including erythema multiforme, headache.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

They are a non-hormonal non-steroidal class of drugs that act on the estrogen receptor (ER). They selectively bind with high affinity to estrogen receptors in various tissues, but act as estrogen antagonist in others. So, it causes endometrial suppression. Ormeloxifene (also known as centchroman) is a selective estrogen receptor modulator.[4] It is a widely used oral contraceptive. It acts by high-affinity interaction with ER, antagonizes the effect of estrogen on uterine and breast tissue and stimulates the effect on vagina, bone, cardiovascular system and central nervous system. It is also effective against advanced breast cancer. In AUB, the treatment of the standard dosage is 60 mg, orally, twice weekly for a period of 12 weeks followed by weekly once in the next 12 weeks. It sometimes lengthen the follicular phase and delays mensturation, can cause dyspepsia, headache and weight gain.

Surgical Management

The role of surgery in the treatment of AUB requires a thorough evaluation of the underlying pathology and patient factors. The medical treatment of heavy menstrual bleeding is effective for many women, and treatment with the LNG-IUS may be comparable to surgical options for improving quality-of-life.

The indications for surgery for women with AUB include:

- Failure to respond to medical therapy, inability to utilize medical therapies (*i.e.* side effects, contraindications),
- Significant anemia, impact on quality-of-life, and concomitant uterine pathology (large uterine fibroids, endometrial hyperplasia). Improvement in quality-of-life, is the ultimate goal of treatment and may occur through achieving eumenorrhea or amenorrhea.

Surgical options for managing AUB depend on several factors including the patient's expectations and uterine pathology. Surgical options include:

- Dilation and uterine curettage,
- Dilation and uterine curettage,
- Hysteroscopic polypectomy,
- Endometrial ablation,
- Myomectomy, and
- Hysterectomy.

Dilatation and curettage, except in cases of severe acute bleeding refractory to medical therapy, should be relegated to a diagnostic technique when endometrial sampling or hysteroscopic evaluation is not possible.

Endometrial ablation is a minimally invasive surgical option for heavy menstrual bleeding. It may be considered in women who have failed medical treatment, have completed childbearing, or who may not be candidate for major surgery. Two methods of endometrial ablation may be offered at the present time. The first method involves hysteroscopic resection and/or ablation. Previously termed 'first generation' endometrial ablation, hysteroscopic-guided endometrial ablation has a significant number of years of reported experience and effective results.

Non-hysteroscopic techniques, or 'second generation' technologies, include a number of varying modalities that all destroy the endometrium without direct visualization.

Radiofrequency-induced Thermal Ablation

It uses radiofrequency electromagnetic thermal energy which destroys endometrium at 66°C. A 0.66 mm metallic probe is inserted transcervically under general anaesthesia and rotated over 360° for 20 minutes. About 85% get cured and 30% develop amenorrhea by end of one year, an occasional uterine perforation or vesicovaginal fistula may occur.

Microwave Endometrial Ablation (MEA)

Microwave energy of 9.2 GHz is generated in a magnetron and is applicated by a probe within the endometrial cavity. It is an outpatient department (OPD) procedure done under local anaesthesia. Temperature of 80°C is used for 3 minutes. There is no need of preoperative endometria thinning.

Balloon Ablation

Singer, et al. reported preliminary experience with a thermal ablation system incorporating a latex intrauterine balloon to treat women with intractable menorrhagia. The balloon is filled with a solution of sterile dextrose and water, and then heated to 83°C for 5 minutes over pressure of 160–180 mm Hg to exert a tamponade effect. About 6 mm of endometrium gets destroyed.

Unipolar Electrodes

The Vesta NHEA system comprises an inflatable balloon that is covered with 12 thermocoupled electrodes. The cervix is dilated to approximately 9 mm, the probe is inserted into the endometrial cavity, and the balloon is inflated allowing the electrodes to make intimate contact with endometrial surface. Activation of electrodes results in a controlled endometrial ablation using a combination of desiccation and coagulation.

Bipolar Electrodes

The NovaSure device is a bipolar instrument designed for performance of NHEA using a combination of electrosurgical vaporization and desiccation/coagulation. The electrodes

are incorporated into the instrument in a way that allows propagation of current and resultant rapid vaporization. Suction is required to remove the steam and carbonized vapor from the endometrial cavity. The instrument is placed into the cavity after dilating the cervix to 8 mm and the electrodes are deployed, and then both suction and electrosurgical energy, the latter from a specially designed and computer-controlled electrosurgical generator.

Risks of endometrial ablation techniques include uterine perforation, infection, hemorrhage, and bowel or bladder injury. Post-ablation syndrome is a condition associated with concomitant or previous tubal ligation and ablation and is a condition of hematometra resulting in cyclical pain with or without hematosalpinx. Risks specific to hysteroscopic techniques include fluid overload, especially with the use of hypotonic solutions (*e.g.* 1.5% glycine), and resulting hyponatremia and its sequelae.

HYSTERECTOMY

Its effectiveness in improving AUB symptoms, being curative and definitive is well-recognized.

Hysterectomy is required:

- If medical management fails or menorrhagia recurs.
- In older women more than 40 years not desirous of pregnancy.

Laproscopic vaginal hysterectomy has quicker recovery, less pain, less abdominal adhesions and evidance of abdominal scar. Lately, vaginal hysterectomy is done for undescended uterus which may even be enlarged.

- Delayed complications, like vault prolapse, sexual dysfunction, chronic abdominal pain due to postoperative adhesions, urinary and bowel symptoms due to ideal NSAID, would be a selective inhibitor of vasodilating prostaglandins (PGs) permitting the vasoconstrictor PGs to inhibit the excessive menstrual blood loss.

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