Treatment Goals of AUB

- Control bleeding
- Prevent recurrence
- Correct anaemia
- Improve quality of life

Any interventions should aim to improve quality of life measures.

Management options of AUB

Medical management

Surgical management

When should we consider medical management ???

if there is : -

- No histological and major structural abnormality
- Fibroids <3cm in diameter causing no distortion of uterine cavity

Medical management is the first line therapeutic option.

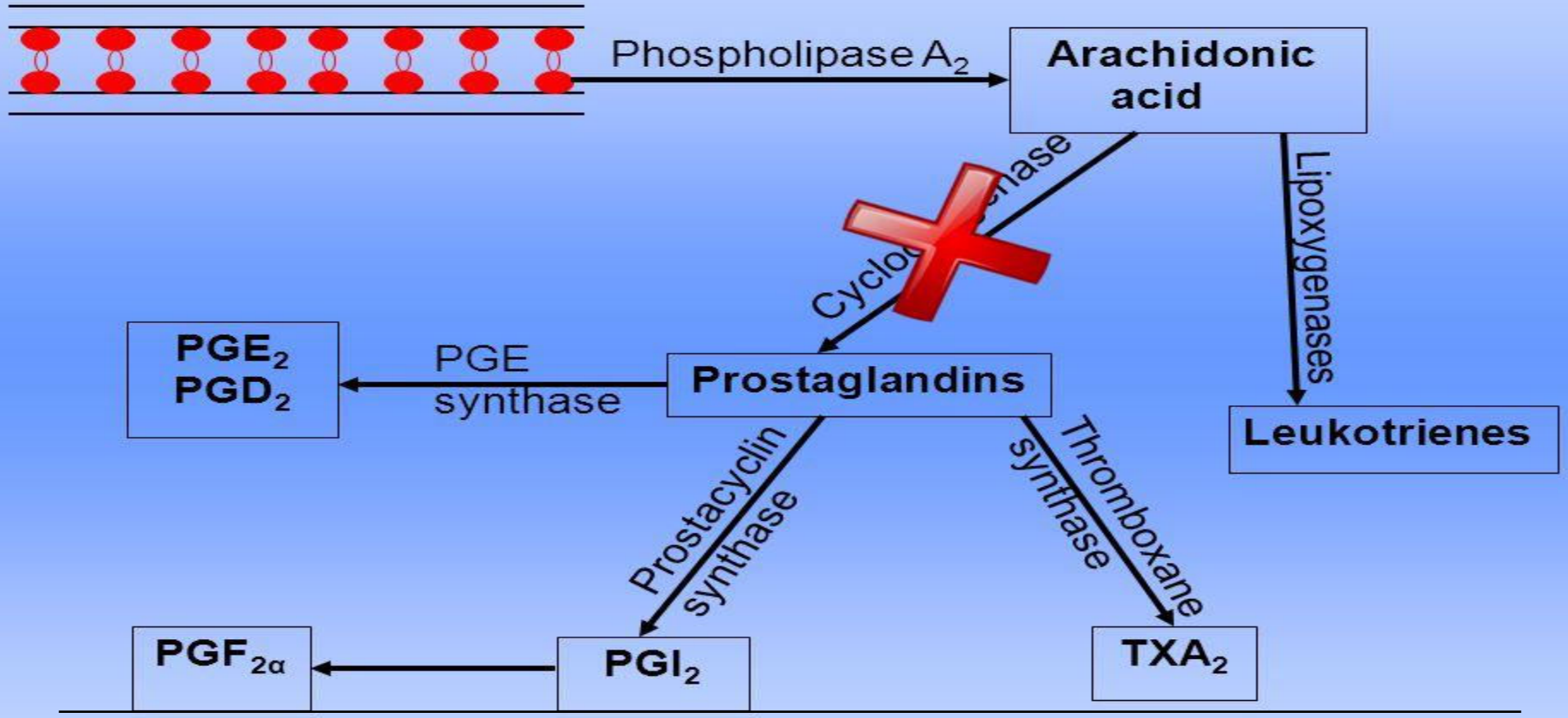
Medical treatment options

- Non-hormonal treatment
- Hormonal treatment

Non-hormonal treatment

Non-steroidal anti-inflammatory drugs (NSAIDs)

Mechanism of action



Non-steroidal anti-inflammatory drugs (NSAIDs)

- Commonly used NSAIDs:- mefenamic acid, ibuprofen and naproxen
- reduced menstrual blood loss by 33% to 55%
- The effect in reduction of menstrual blood loss is comparable to COC and progestins.
- Less effective than tranexamic acid and LNG-IUS
- No individual variations among NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs)

- additional benefit of improving dysmenorrhea for up to 70%
- Start at the first day of menses and continued for 5 days or until cessation of menstruation
- If it does not improve symptoms within 3 menstrual cycles, stop treatment.

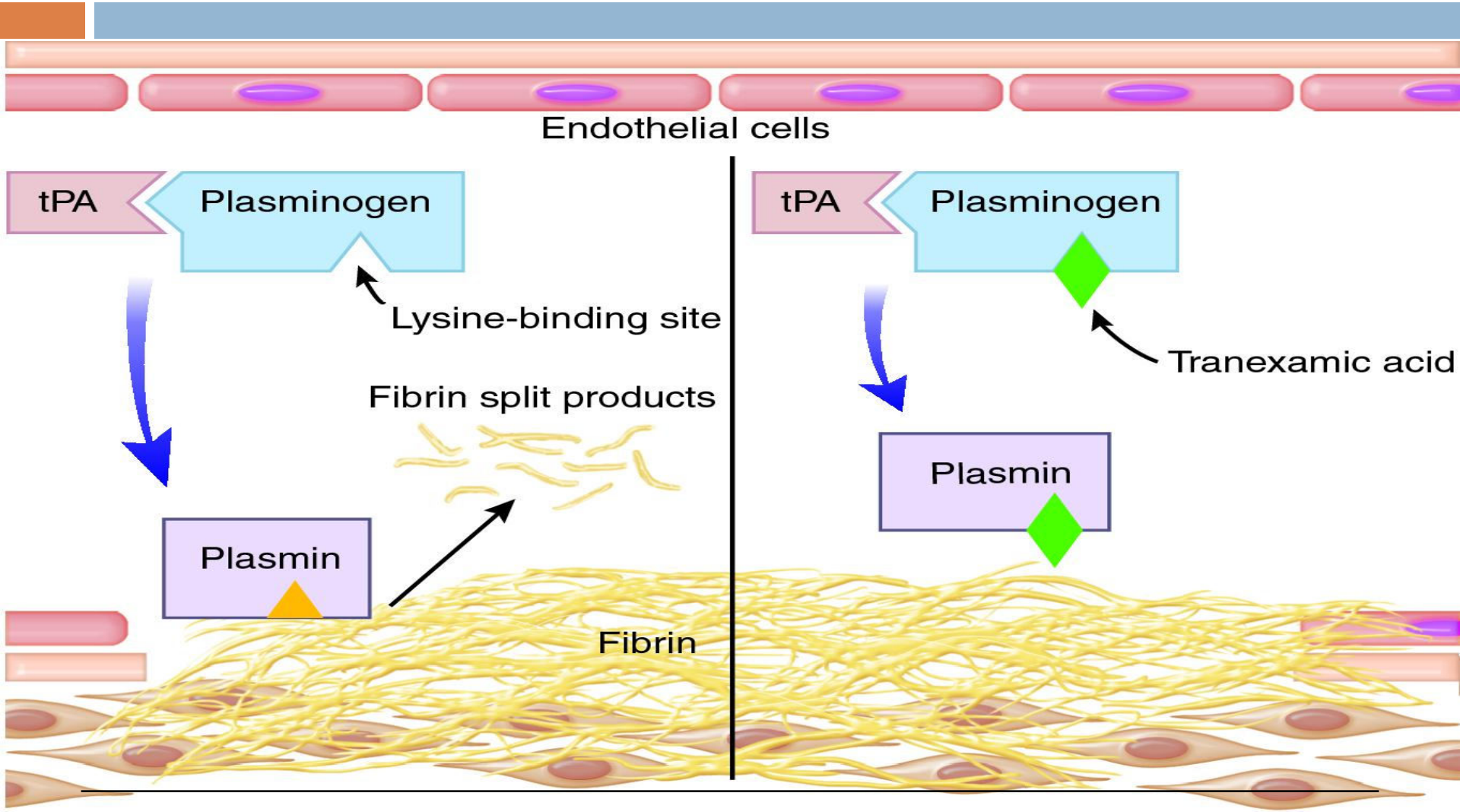
Non-steroidal anti-inflammatory drugs (NSAIDs)

- Adverse effects : nausea, vomiting, abdominal pain, headache
- contraindications : women with bleeding disorders or platelet function abnormalities

Antifibrinolytic agent (Tranexamic acid)

- Synthetic derivative of lysine
- Tranexamic acid is an anti-fibrinolytic drug that reduces blood loss given only with menstruation in women with heavy menstrual bleeding.

Antifibrinolytic agent (Tranexamic acid)



Source: Barbara L. Hoffman, John O. Schorge, Karen D. Bradshaw, Lisa M. Halvorson, Joseph I. Schaffer, Marlene M. Corton: *Williams Gynecology*, 3rd Edition: www.accessmedicine.com

Antifibrinolytic agent (Tranexamic acid)

- Recommonded dose : one gram orally every 6 hours for the first four days of the cycle
- Intravenous tranexamic acid is available for more acute scenarios, with a dose of 10 mg/kg every 6 hours.
- Reduce the menstrual blood loss by up to 40%
- does not treat dysmenorrhea

Antifibrinolytic agent (Tranexamic acid)

- If tranexamic acid does not decrease menstrual blood loss within 3 cycles, it should not be continued.
- Side effects are usually mild, but may include nausea, vomiting, diarrhea, and headaches.
- The risk of venous thromboembolism by tranexamic acid is controversial.
- Regardless of the lack of evidence, antifibrinolytics should be used with caution in patients with risk factors for thrombosis or when prescribed with CHCs.

Antifibrinolytic agent (Tranexamic acid)

- Tranexamic acid and NSAIDs can be used together but should be stopped after 3 months if there is no symptomatic improvement.
- If they are beneficial, they may be continued indefinitely.
- They can also be used as adjuvant therapy with hormonal preparations.

Hormonal treatment

Combination hormonal contraceptives (CHCs)

Excellent choice for women with abnormal bleeding who are seeking a reliable method of contraception

- **progesterone component** – suppress ovulation, inhibits ovarian steroidogenesis and create endometrial atrophy

- **Estrogen component -** supports to the endometrium to reduce unscheduled breakthrough bleeding

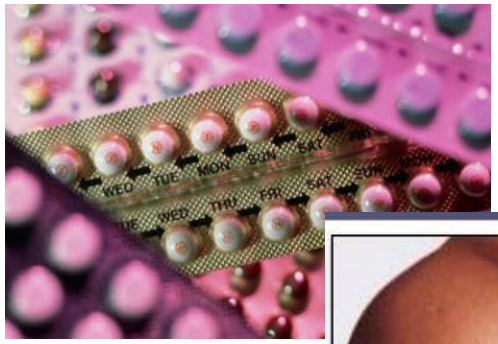
Combination hormonal contraceptives (CHCs)

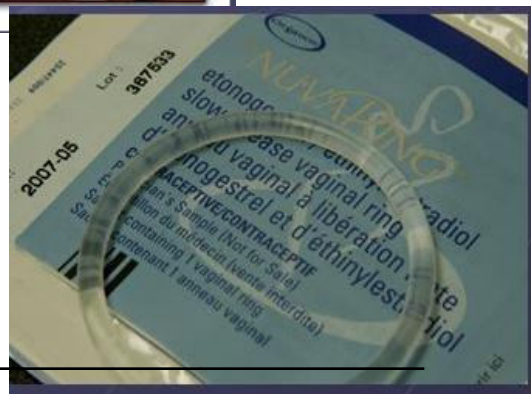
- excellent cycle control
- significantly reduce menstrual loss (up to 40% to 50%)
- improve dysmenorrhea

Combination hormonal contraceptives (CHCs)

Types of CHCs

- oral contraceptive pill
- contraceptive patch
- vaginal ring





All CHCs are effective in reduction of menstrual blood loss.

Combined hormonal contraceptives (CHCs)

Regiemes

- **21 days, followed by 1 pill free week**

  reduce MBL up to 40-50%

- **Continuous use of CHCs without the hormone-free interval**

  induce amenorrhea in 80–100% of women by 10–12 months

Combination hormonal contraceptives (CHCs)

The possible side effects

- breast tenderness
- mood change
- headache
- nausea
- vomiting

Contraindications

- women who are over 35 yrs old who smoke
- hypertension
- cardiovascular disease
- migraine with aura
- breast cancer
- venous thromboembolism or thrombogenic mutation

Progestins

- Safer alternatives for women with fewer contraindications compared to CHCs

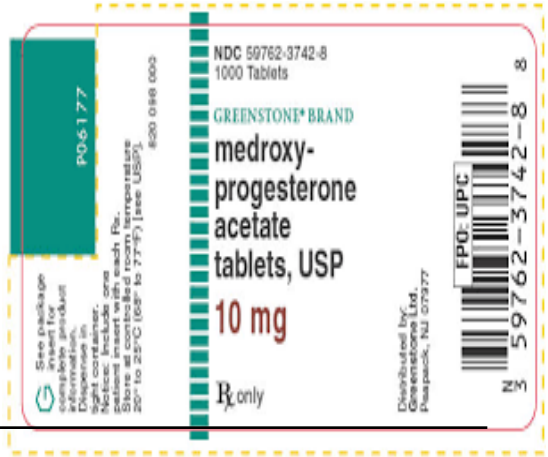
- **Oral progestin** - norethindrone acetate (NETA)
  medroxyprogesterone acetate (MPA)

- **Injectable progestin** - medroxyprogesterone acetate (Depo-Provera)

Progestins

Oral progestin

- Long-course (21 days per cycle) reduced MBL in 63–78% of the women
- Short-course luteal phase progestin does not produce significant benefit.
- Possible adverse effects : - unscheduled bleeding, headache, breast tenderness, nausea and vomiting



Progestins

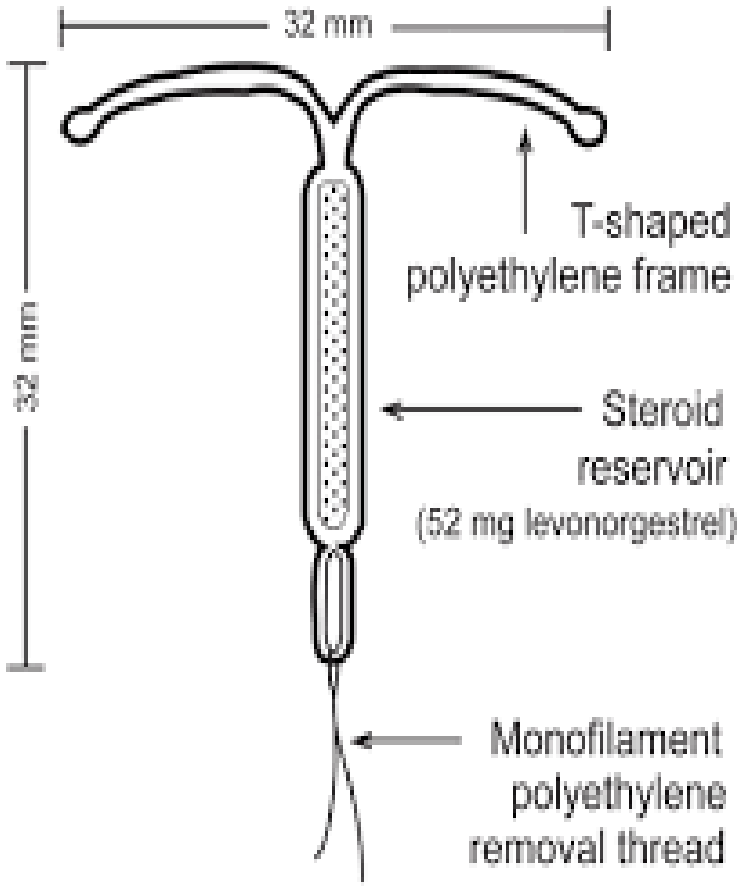
Injectable progestin

- induces amenorrhea by inhibition of FSH thus inhibiting follicular development, reducing estradiol synthesis and secretion resulting in a thin endometrium
- Administered every 12 weeks
- In trials, over half of the women became amenorrheic after 1 year, but many reported unscheduled bleeding in the first few months.
- excellent contraception

Progestins

Progestin intrauterine system (LNG-IUS)

- ***First line of treatment in AUB (NICE, 2007)***

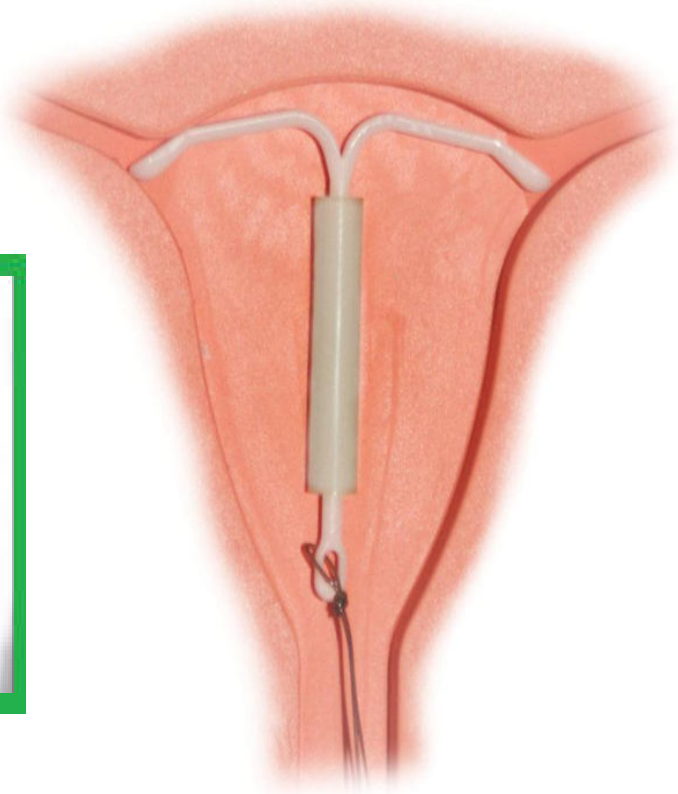


Source: Berlex Laboratories.

Progestins (LNG-IUS)

Vertical stem: release daily doses of 20 micrograms of LNG

Effects:
-prevent endometrial proliferation
-thicken cervical mucus
-suppress ovulation



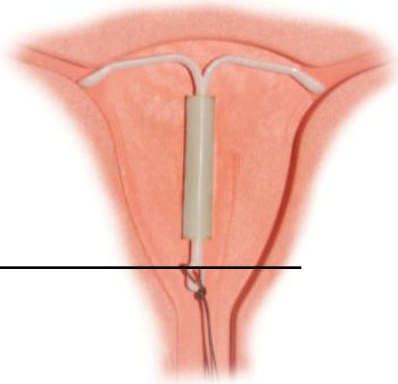
Reduction of MBL between 71-96%
-benefit seen after 6 months

Requires an endometrial cavity that is 6 to 9 cm in length with minimal distortion

Progestins (LNG-IUS)

- Approved for heavy menstrual bleeding treatment for up to 5 years

- Minimal concentrations of LNG are absorbed into the systemic circulation (0.4 to 0.6 nmol/L), limiting the likelihood of systemic hormonal side effects.



Progestins (LNG-IUS)

- amenorrheic by 12 months
- Changes in the bleeding pattern lasting for longer than 6months, particularly in first few cycles
- Should be advised to preserve for at least 6 cycles to see the benefits of the treatment

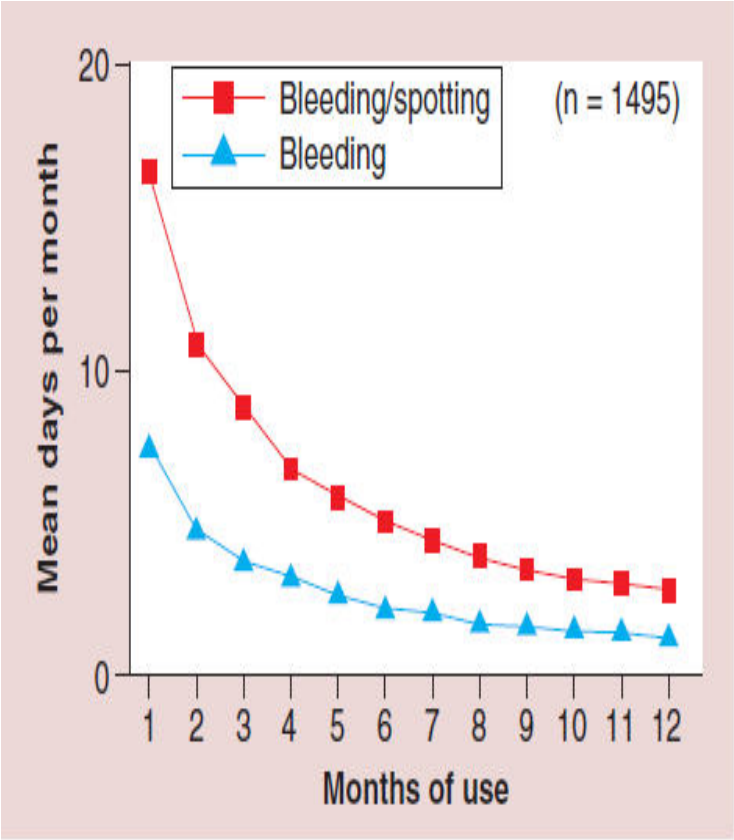


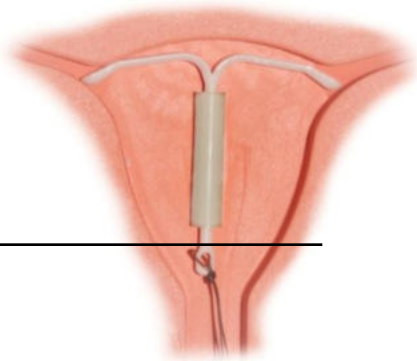
Figure 3. Impact of levonorgestrel-releasing intrauterine system on bleeding and spotting in the first year of use.

Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. Contraception 49(1), 56–72 (1994).

Progestins (LNG-IUS)

Drawback:

- high cost
- spontaneous expulsion (7%)
- uterine perforation (1:1000 cases)



Progestins (LNG-IUS)

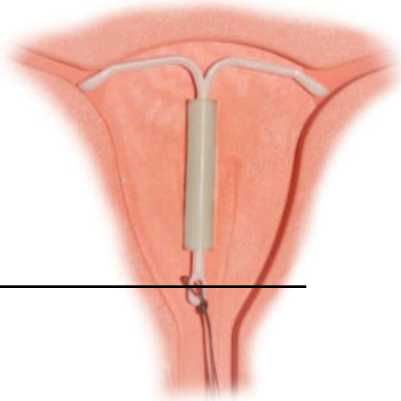
- Common side effects

  unscheduled bleeding, breast tenderness, abdominal/pelvic pain/back pain, headache, ovarian cyst, and acne

- Contraindications

  pregnancy, unexplained vaginal bleeding,

  uterine sepsis



Danazol

- Synthetic steroid with androgenic properties
- Anti-estrogenic and anti-progestogenic effect
- Can reduce the menstrual blood loss up to 80%

Danazol

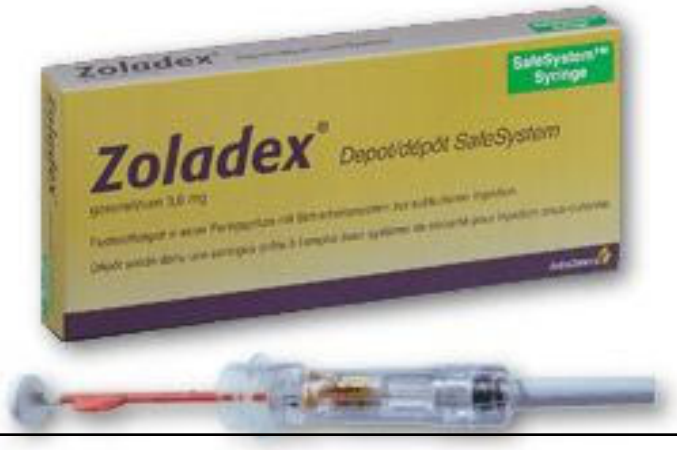
- 100 to 400 mg/day in divided doses
- 20% of women will become amenorrheic and 70% reported oligomenorrhoea.
- The side effects:- androgenic effects such as hot flushes, myalgia, weight gain and acne, which occur in 85% of users.

Danazol

- significantly more adverse effects than other medical therapies
- should not be used routinely
- should be limited to 6 months

GnRH agonists

Synthetic peptide that act like a natural GnRH but with longer biological half life



GnRH agonists

Binds to GnRH receptor
Decreased FSH and LH

No follicular development, estrogen production, no ovulation, no progeterone, no menses

GnRH agonists

- endometrial atrophy and amenorrhoea within 3–4 weeks following initiation of treatment
- amenorrhea rate of up to 90%
- relief from dysmenorrhea associated with adenomyosis and endometriosis
- increase the haematocrit level with minimal side effects

GnRH agonists

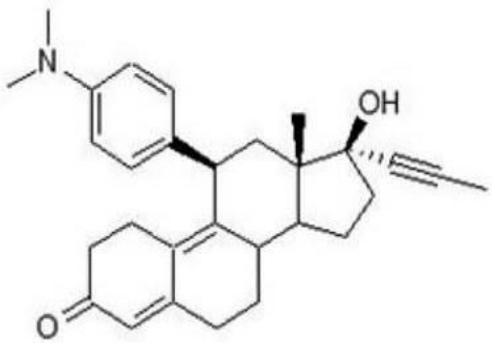
- reduce uterine and leiomyoma volume by up to 60% (reverses within months of stopping Rx)
- Use as short-term preoperative therapy
- adverse effects in long-term: bone pain, loss of bone density, hot flashes, night sweats and vaginal dryness
- Add-back therapy with low-dose estrogen and progestins (beyond 6 months of treatment)

GnRH agonists

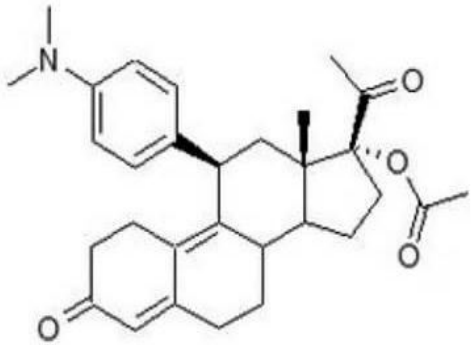
- The long-term use of GnRH agonists in abnormal bleeding should be limited if other medical or surgical treatments are contraindicated.

- the possible temporary “flare” or exacerbation of symptoms immediately after GnRH injection

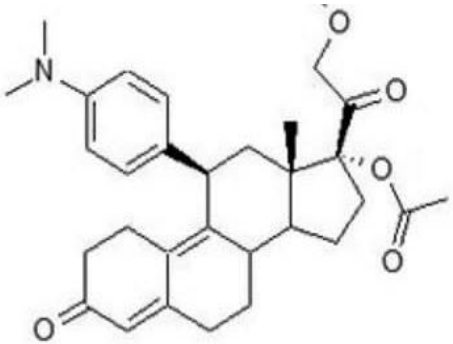
Selective progestrone receptor modulators(SPRM)



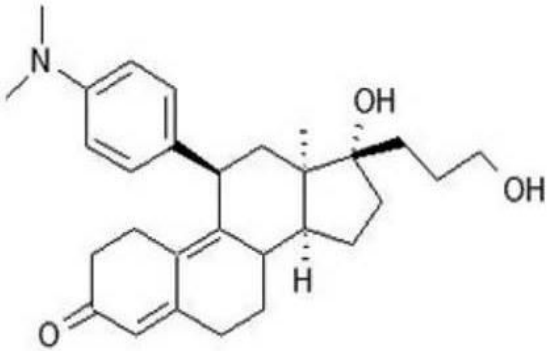
RU-486 / Mifepristone



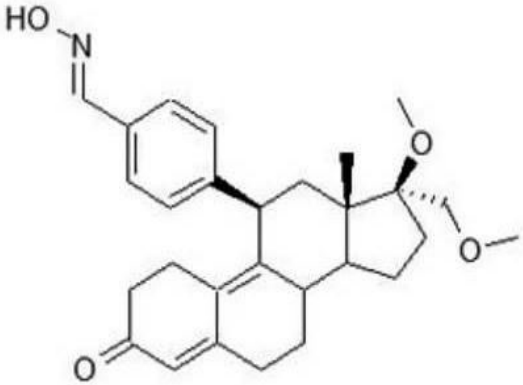
Ulipristal



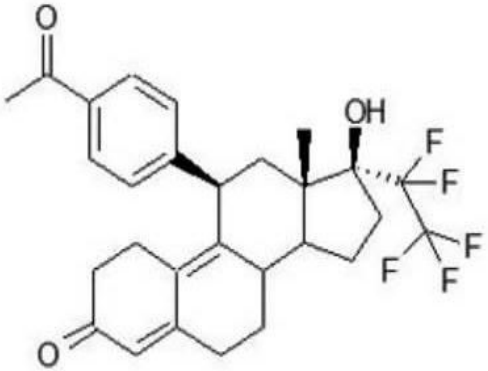
Proellex



Onapristone



Asoprisnil



Lonaprisan

Selective progestrone receptor modulators (SPRM)

- Ulipristal acetate – the only SPRM to have been licensed for use in clinical practice
- Tissue specific partial progesterone antagonist effect and modulates the progesterone receptors in endometrium and underlying myometrial tissue resulting proapoptotic / antiproliferative effects on fibroid cells

Selective progestrone receptor modulators (SPRM)

- Control of heavy menstrual bleeding in 90% of women
- Amenorrhoea in over 70% of women
- Median times to amenorrhea: - 7 days for patients receiving 5 mg of ulipristal acetate
- Progestrone receptor modulator associated endometrial changes (PAEC) - benign, non-physiological, non-proliferative, histological features of the endometrium
- spontaneously reverse over a few weeks to months after cessation of the 3-month UPA treatment.

Selective progestrone receptor modulators (SPRM)

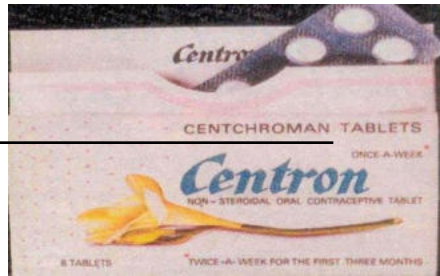
- Median reduction in size of fibroids (12-36%)
- After treatment cessation, menstruation usually returns within 4–5 weeks, but fibroid volume reduction can be sustained for up to 6 months.
- Given as short-term (3 months) pretreatment of fibroid prior to surgical removal (5-10mg daily)

Selective progestrone receptor modulators (SPRM)

- Minor reported side effects – headache (4%), breast complaints (4%)
- Short-term use of SPRMs resulted in improved quality of life, reduced menstrual bleeding and high rates of amenorrhoea.
- No publication to date on the clinical utility of SPRMs in the management of women with heavy menstrual bleeding without fibroids

Selective estrogen receptor modulators (SERM)

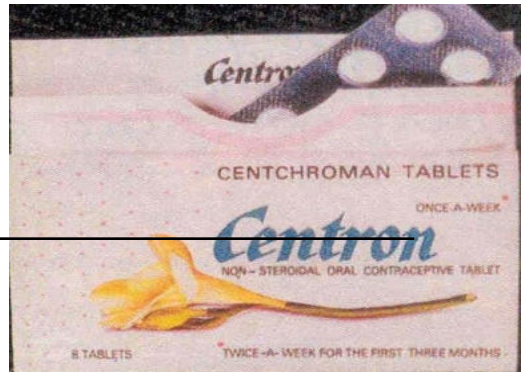
- Ormeloxifene is a selective estrogen receptor modulator, which significantly inhibits endometrial proliferation and increase haematocrit level among HMB women.
- With a dose of 60 mg twice a week
- Reduce the menstrual blood loss and endometrial thickness by 85-97.7%
- after 3 months of treatment, 9.5% of the women reporting amenorrhea



Selective estrogen receptor modulators (SERM)

- Side effects :- headache, GI upset, ovarian cyst
- Avoid in liver and renal disease, PCOS
- Benefit - cost effective, convenient dosage, any age group, protective to breast and endometrium, use as contraception

More RCTs required.



Medical treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	Treatment
AUB-P (Polyps)	▪ Multiple polyps or polypoidal endometrium and fertility is not desired– LNG-IUS can be combined with surgical removal
AUB-A (Adenomyosis)	▪ LNG-IUS ▪ If LNG IUS is not accepted– CHCs, NSAIDs, progestins ▪ GnRH agonists with add back therapy

Medical treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	Treatment
AUB-L (Leiomyoma)	▪ Tranexamic acid or CHCs or NSAIDs, LNG-IUS ▪ In women >40 years of age, fertility is not desired, short-term management (up to 6 months)– GnRH agonists followed by hysterectomy ▪ In women <40 years of age, fertility is desired, short-term management of GnRH agonists followed by myomectomy ▪ Long-term GnRH with add-back therapy
	▪ Newer medical options: SPRMs

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Medical treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	Treatment
AUB-M (Malignancy and Endometrial Hyperplasia)	Hyperplasia without atypia : - ▪LNG-IUS ▪oral progestins ▪SPRMs
AUB-C (Coagulopathy)	▪Tranexamic acid as primary option ▪Hormonal treatment with CHCs/LNG-IUS as secondary option ▪NSAIDs and injectables were contraindicated.

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Medical treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	Treatment
AUB-O (Ovulatory Dysfunction)	▪ In women desiring contraception; - COC, DMPA, and LNG-IUS ▪ In women with cyclic bleeding or predictable in timing;- NSAIDs and antifibrinolytics
AUB-E (Endometrial)	Similar to management of AUB-O

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Medical treatment options for abnormal uterine bleeding based on PALM-COEIN etiology

Etiology	Treatment
AUB-I (Iatrogenic causes)	▪ Medications causing AUB should be changed to other alternatives ▪ If no alternatives are available, LNG-IUS is recommended.
AUB-N (Not defined)	▪ Idiopathic AUB and desire effective contraception:- LNG-IUS and CHCs ▪ Cyclic oral progestins (from day 5 to 26), are recommended if CHCs are contraindicated. ▪ Cyclic bleeding :- NSAIDs and Tranexamic acid ▪ If medical and surgical treatment have failed or contraindicated:- GnRH with add-back therapy

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