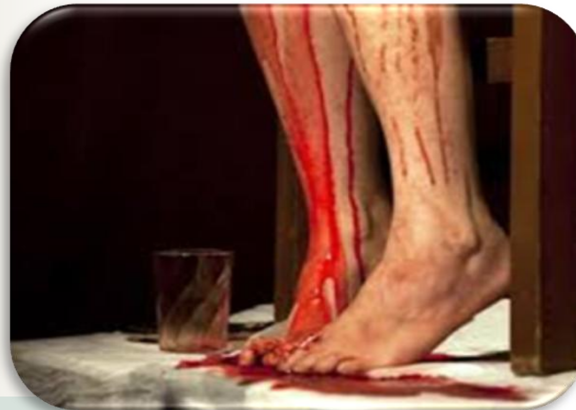
Management of AUB & HIRSUTISM In Patients With PCOD



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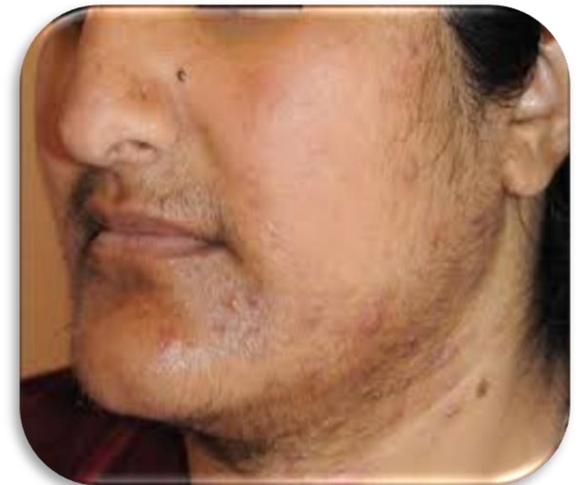
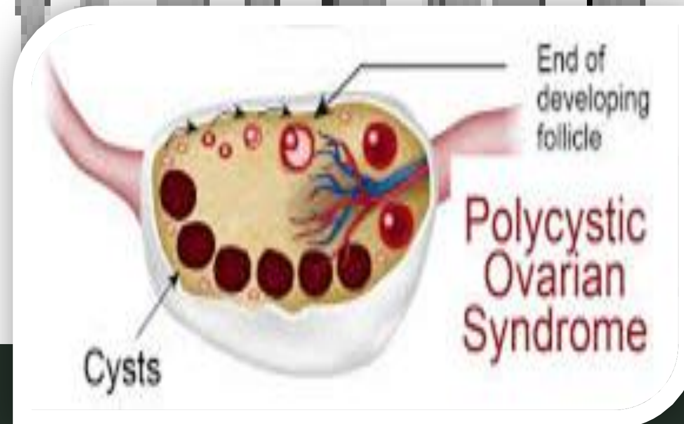




The most common endocrine disease

The incidence →5–15%

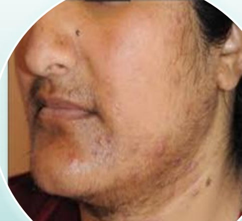
in reproductive-aged women

❑The *diagnostic Rotterdam Criteria (2003)*

***TWO** out of 3 features:*

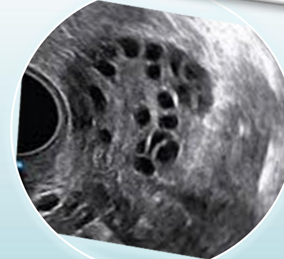
Menstrual Irregularities

(%60-85)



Hyperandrogenism

(%60-70)



Polycystic ovaries on ultrasound

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(PCOD adult phenotypes)

Phenotype 1 (classic PCOS)

Clinical &/or biochemical evidence of hyperandrogenism
Evidence of oligo-anovulation
Ultrasonographic evidence of a polycystic ovary

Phenotype 2 (hyperandrogenic anovulation)

Clinical &/or biochemical evidence of hyperandrogenism
Evidence of oligo-anovulation

Phenotype 3 (ovulatory PCOS)

Clinical &/or biochemical evidence of hyperandrogenism
Ultrasonographic evidence of a polycystic ovary

Phenotype 4 (non- hyperandrogenic PCOS)

Evidence of oligo-anovulation
Ultrasonographic evidence of a polycystic ovary

Abnormal uterine bleeding in PCOD (AUB)

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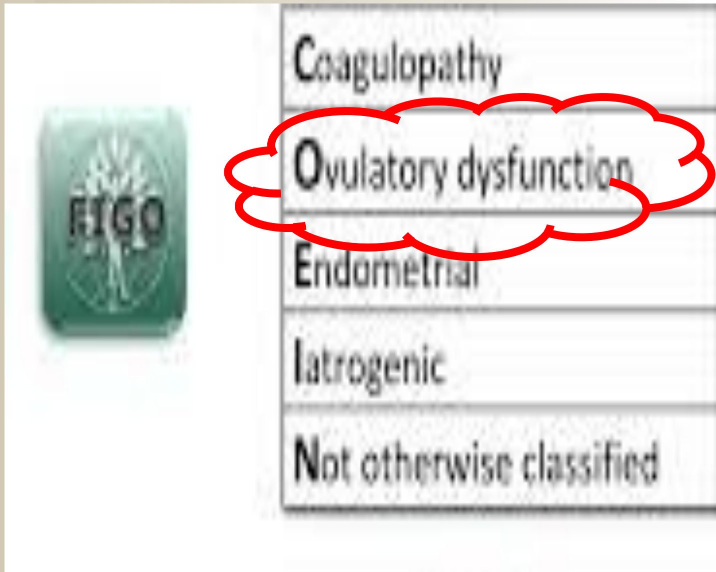
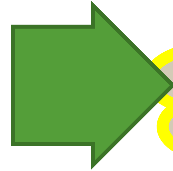
Abnormal Uterine Bleeding: New FIGO Classification

Polyp
Adenomyosis
Leiomyoma
Malignancy & hyperplasia

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not otherwise classified

Abnormal Uterine Bleeding: New FIGO Classification





Heavy /prolonged / Irregular bleeding in patients with ovulatory dysfunction

(AUB-O)

(AUB-O)
in PCOD

- It begins in the peripubertal period
  - developing oligomenorrhea at a much later age , less likely in PCOD
  - associated with delay in menarche

Abnormal menstrual pattern

- **oligomenorrhea** (**<u><9</u>** menstrual periods in a year)
- **Amenorrhea** (No menstrual periods **<u>>3</u>** consecutive months) (less often)
- Regular cycles after age **40** years
- poly menorrhea (uncommon)

Indications for treatment (AUB-O) in PCOD

1st step

The etiology should be identified.

- R/o other causes

RX of underling problem (PCOD) may restore cyclic menses.

2nd step

The goals of RX :

- to establish a regular menses (or amenorrhea)
- to prevent heavy bleeding
- to prevent endometrial hyperplasia / CA.
- RX of infertility
- RX of anemia
- Restoring of life quality

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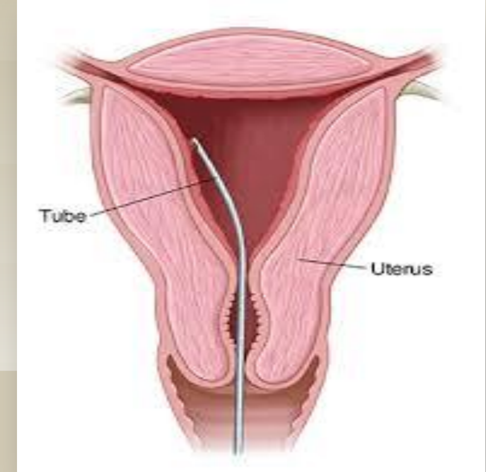
Prior to start treatment

1- endometrial hyperplasia /CA.
2- pregnancy related events

Indications of Endometrial Sampling



1 - chronic anovulation
(focus on concomitant risk factors: obesity, D.M, hyperandrogenism)

2 - No response to appropriate empirical medical therapy

3 - An episode of profuse uterine bleeding
(to exclude endometrial neoplasia / endometritis)

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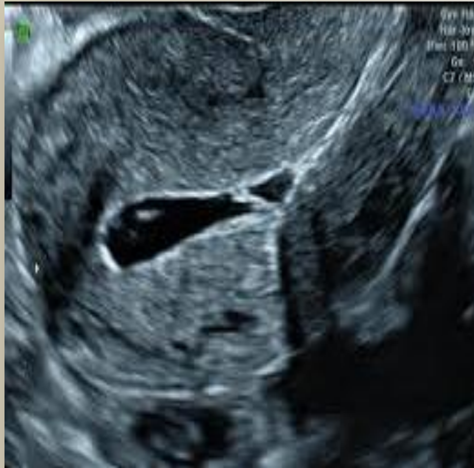
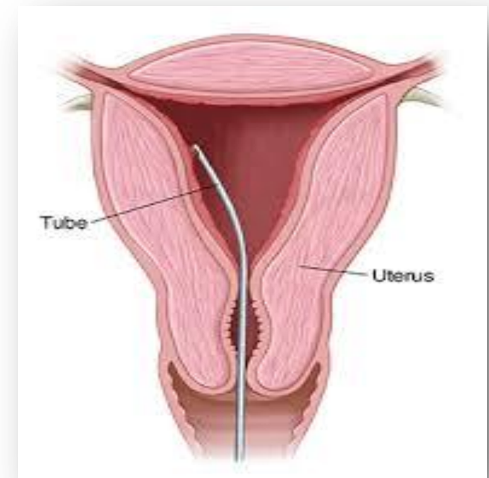
Endometrial Sampling

- **(E.T > 12 mm)**
is suggesting the possibility of endometrial hyperplasia .

- **(E.T= 5-12mm)**
NL thickness does not exclude the diagnosis .



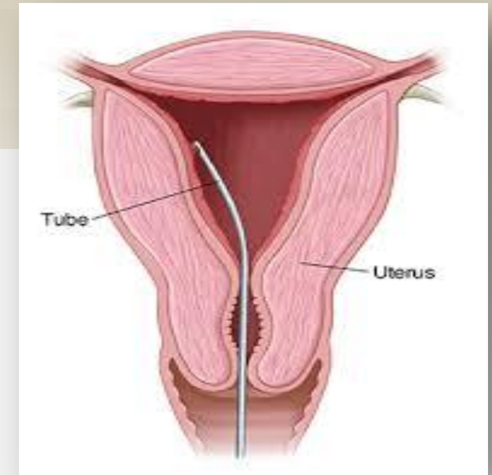
- **(E.T ≥ 5 mm)**
+
1 / 2 / 3



1 -Endometrial sampling

2- SIS + End . BX

Endometrial Sampling



➢ **Timing of sampling :**

before, during, after RX
(depends upon the choice of initial RX)

➢ It is preferable to collect the specimen prior to hormonal therapy

➢ Hormonal alterations may interfere with interpretation of the sample

Lifestyle changes

_20 -27 KG/ M2_

Medical treatment (AUB-O)

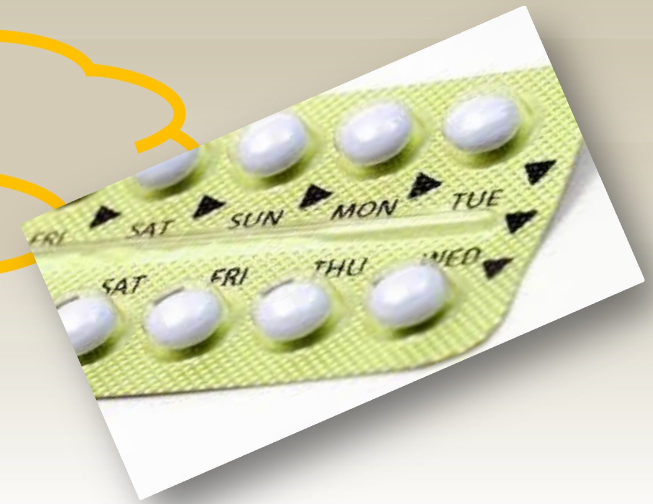
Anovulation

Unopposed Estrogen condition

Insufficient progesterone secretion

AUB-O

Medical treatment (AUB-O)



1st - line therapy

- **1- Estrogen-progestin contraceptives** (ORAL AGENTS)

- contraceptive effect in sexually active PCO women
- regulating bleeding, decreasing hirsutism
- providing endometrial protection
- **NO** evidence that women with PCOD are at greater risk for
    - Metabolic adverse effects
    - Cardiovascular complications
- caution about withdrawal bleeding

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Medical treatment (AUB-O)

1st - line therapy

- **1-** The Choice of oral contraceptive :

An OC containing 20 mcg of ethinyl estradiol combined with

- A progestin with minimal androgenicity **(Norgestimate)**
- Other progestins with minimal androgenicity / antiandrogenic properties **(Desogestrel / Drospirenone / dienogest)**

(Both have been associated with a POSSIBLE higher risk of VTE)

Medical treatment (AUB-O)

1st - line therapy

- **1-** The Choice of oral contraceptive :

OCs containing 20-35 mcg of ethinyl estradiol combined with one of the original progestins (Norethindrone / Norethindrone acetate)

(They are not as low in androgenicity & not been associated with excess VTE risk)

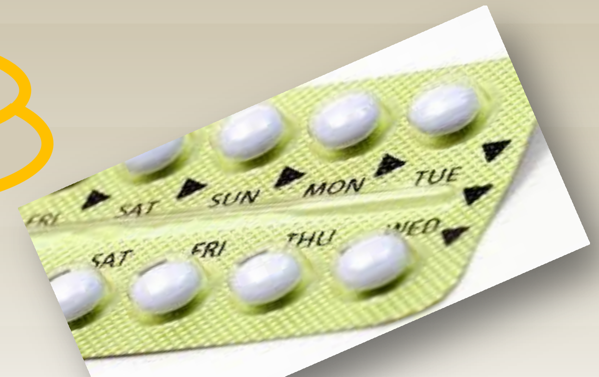
Medical treatment (AUB-O)

❑ Other combined contraceptive agents :

Transdermal & vaginal combined formulations provide:
- regular menstruation
- endometrial protection

(They been associated with **excess** VTE risk)

Medical treatment (AUB-O)

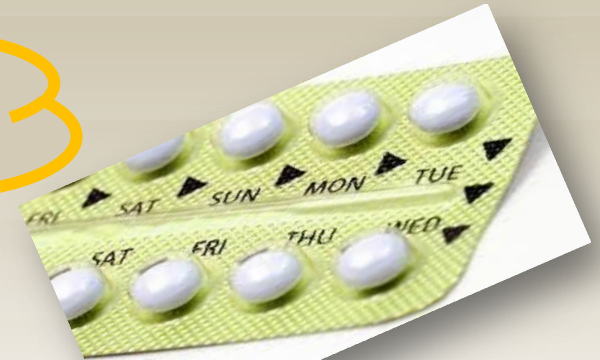


1 - Estrogen-progestin contraceptives

OCs may be prescribed:

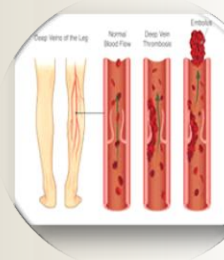
cyclic	extended	continuous
• **Monthly withdrawal bleeding**	• **withdrawal bleeding every 3 months**	• **no withdrawal bleeding** • more effective • breakthrough bleeding

Medical treatment (AUB-O)

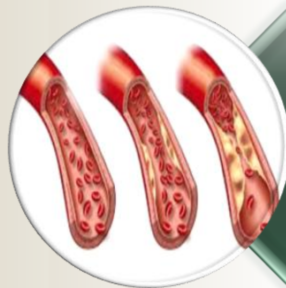


1 - Estrogen-progestin contraceptives

Potential complications of estrogen therapy



thromboembolism (VTE)



coronary / cerebral thrombosis

Medical treatment (AUB-O)

1 - Estrogen-progestin contraceptives

absolutely contraindicated in women at high risk of such complications:

current or a personal HX of :

- Inherited thrombophilia
- Myocardial infarction
- Cerebrovascular accident
- Malignancy

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Medical treatment (AUB-O)

1 - Estrogen-progestin contraceptives

Relative contraindication to estrogen therapy

HTN	D.M	S.L.E
Age > 40	Obesity	Smoking

*PCOD is **NOT** an additional independent risk factor for VTE*

Medical treatment (AUB-O)

1 - Estrogen-progestin contraceptives

The approach to the use of OCs in PCOD is the same as in non PCOD women

Prescribe Ocs with caution to obese women ([BMI] ≥ 30 kg / m^2) with age >40 years

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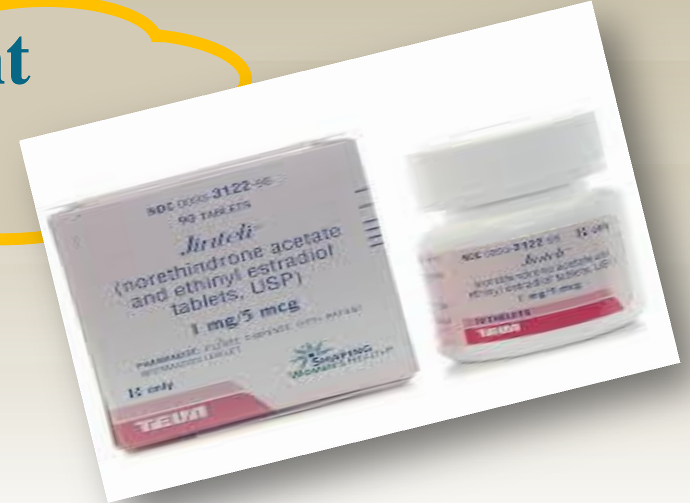
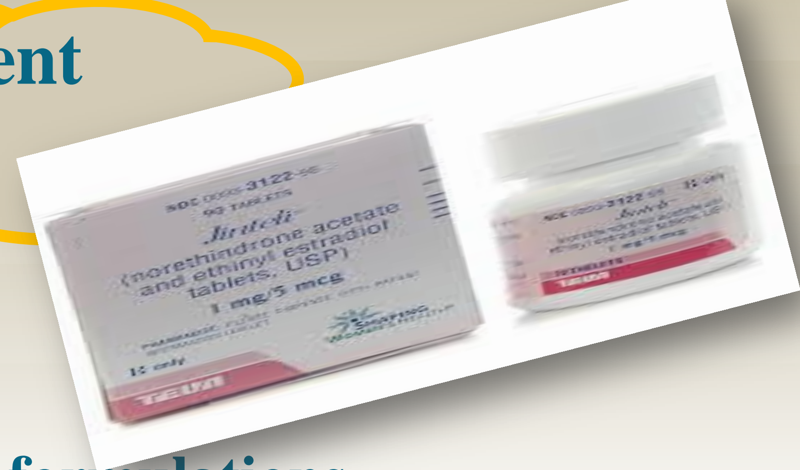
Medical treatment (AUB-O)



- **Noncontraceptive estrogen-progestin formulations**
  - Off-label use of ultra-low estrogen dose formulations (relief of menopausal symptoms)
  - AUB & relative contraindications to contraceptive doses of estrogen:

Medical treatment (AUB-O)



- Noncontraceptive estrogen-progestin formulations

  - dosage < the typical OC dose **(20 - 35 mcg ethinyl estradiol)**

-NO contraceptive effect

(Jinteli 1/5)

(ethinyl estradiol 5 mcg + norethindrone acetate 1 mg)

- approved for RX of vasomotor symptoms in menopausal patients
- Each pack contains 28 days of hormonally active tablets (continuous therapy)
- often resulting in amenorrhea after several months

Medical treatment (AUB-O)

1 - Estrogen-progestin contraceptives

Before starting estrogen containing drugs in women with risk factors for thrombosis :

The patient should be counseled about the risks of RX →	warning about signs of thrombosis : - **asymmetric swelling of extremities** - **chest pain** - **shortness of breath** →	Monitoring for these symptoms

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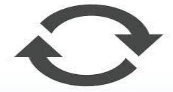
Medical treatment (AUB-O)



1st - line therapy

2 - oral progestin therapy

Cyclic oral progestins :

oral medroxyprogesterone acetate

(5 -10 mg /day× 10 - 14days/ 1 -2 months)

(20 -40 mg / day in acute episodes, tapering to 5mg/day ×21- 60 days)

- moderate & predictable withdrawal bleeding
- no contraceptive effect
- occasionally irregular bleeding (Random ovulatory cycles)

↓ bleeding

↓ the risk of endometrial hyperplasia / CA

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Medical treatment (AUB-O)

Continues oral progestins (minipills):

(<u>norethindrone</u> 0.35 mg/day)

(<u>drospirenone</u> 4 mg / day)

Breakthrough bleeding in the patient who complains about AUB

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Potential complications of progestin therapy

Epidemiologic studies **HAVE NOT** identified an increased risk of stroke, MI , DVT with progestins .

Norethindrone can be converted to ethinyl estradiol .

The use of high dose of this progestin should be avoided in at risk patients .

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Medical treatment (AUB-O)

high-dose oral progestins

(<u>norethindrone</u> 5 mg tablets, 1-3/day)

continue the dose until ↓ bleeding

taper the dose to minimal effective dose (2.5-5 mg, (1/2-1 of tablet / day)

- no effect on pregnancy occurring during usage
- continue cyclic low –dose progestin agents

Only in the patient with ACUTE EPISODE of sever vaginal bleeding

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Medical treatment (AUB-O)

Continues potent oral progestins :

Oral agents (**Megestrol acetate 20- 40 mg ×2 / day**)

- **ONLY** should be used in acute bleeding
- continue till 3weeks & tapering after7-10days
- continue cyclic progestin agents

- Breakthrough bleeding
- Side effect of potent progestins :

- **Acne**
- **Weight gain**
- **Lipid& B.S abnormalities**
- **Mood changes**
- **Bloating**
- **Increased appetite**

Medical treatment (AUB-O)

Implants containing progestins :

- **Etonogestrel implant (Nexplanon)**
- **Levonorgestrel implants (Jadelle , Norplant , sinoplant II)**

Breakthrough bleeding in the patient who complains about AUB

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Medical treatment (AUB-O)

Depot medroxyprogesterone acetate

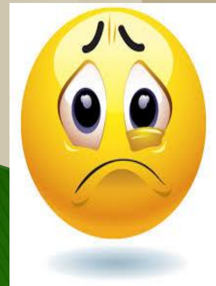
(150 mg / 3 months)

Appropriate for patients with AUB &:

1 - contraindications to or prefer to avoid estrogen

2 - having a desire to this method of contraception

The contraceptive effect persists for > the 3-month dosing interval



NOT an option for patients , interested in conceiving (next 1 -2 years)

- Episodic breakthrough bleeding

Medical treatment (AUB-O)

1st - line therapy

3- Levonorgestrel IUS (LNG -IUS)

- perfect contraceptive effect
- ↓BLOOD LOSS & amenorrhea (overtime) (2/3 of the users)
- Endometrial protection
- Can be left for 5-6 years
- Easy to use
- Immediately resumption of fertility after removal
- A good choice in :
  - PCOS ,obese women with / without medical illness
  - Poor toleration / contraindication for systemic hormones

- **NOT** providing regular menstruation

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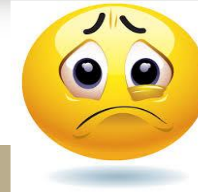
Medical treatment (AUB-O)

1st - line therapy

3- Levonorgestrel IUS (LNG 52)

- ➢ ↓ bleeding
- ➢↓ the risk of endometrial hyperplasia / CA



- ➢By package labeling contraindicated in congenital / acquired distortion of the endometrial cavity
- ➢ IUS insertion by ultrasound guiding in cases with cavitary distortion

Medical treatment (AUB-O)

Breakthrough Bleeding

- An complication of prolonged use of any component containing progestin agents
- A result of thin endometrium

- Short interval estrogen therapy

  1- Conjugated estrogen 1.25 mg

  2- micronized estradiol 2 mg × 7-10days

- D/C progestin agent for short time
- Increase dosage of estrogen

Medical treatment (AUB-O)

2nd - line therapy

1- Tranexamic acid

- an antifibrinolytic agent
- competitively blocks conversion of plasminogen to plasmin
- reducing fibrinolysis

- useful in conjunction with hormonal therapy in an acute episode of **HEAVY BLEEDING**

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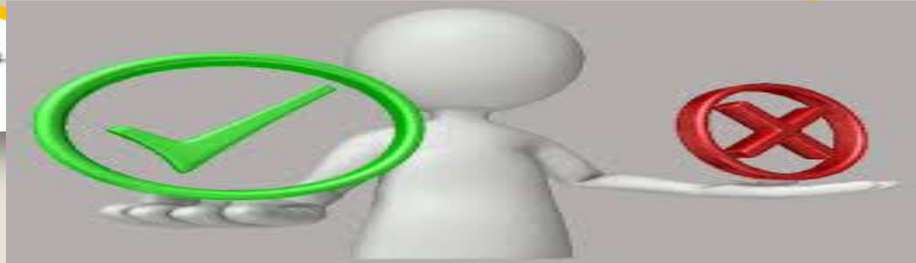
Medical treatment (AUB-O)



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- Could be used while trying to conceive
- Taken only during menses
- useful in contraindication for hormonal therapy
- useful in conjunction with hormonal therapy

- Controversy in DVT risk
- better to reserve for short-term therapy (RISK OF DVT in long-term use)
- anemia is associated with an ↑ RISK of thrombosis (**result of reactive thrombocytosis**)
- menstrual cramps , back pain

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Medical treatment (AUB-O)

2nd - line therapy

The short-term use is appropriate with using combined hormonal contraceptives, without additional thrombosis risk factors :

(eg, obesity, immobility, coagulopathy)

Medical treatment (AUB-O)

2nd - line therapy

Dosage Calculations

- **In patients with NL renal function**
  - 1300 mg (2× 650 mg tablets) 3 times/ day (FDA approval dosage)
    a total of 3900 mg for 5 days (during menstruation)
  - 1000 -1500 mg × 3-4 times / day

- **In patients with impaired renal function**
  the dose should be adjusted according to the package insert

NO contraindication to concurrent use of **NSAIDs** & **tranexamic acid**

Medical treatment (AUB-O)

2nd - line therapy

Nonsteroidal anti-inflammatory drugs

- a nonhormonal, noncontraceptive option
- Reducing menstrual blood loss by ↓ PGE2 & PGF2∝
- leading to vasoconstriction & ↓ bleeding
- effective in HMB
- **NOT** typically used to treat AUB-O

Medical treatment (AUB-O)

2nd - line therapy

Nonsteroidal anti-inflammatory drugs

-NSAIDs used to treat HMB :

Ibuprofen

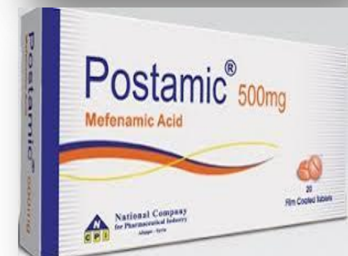
600 mg once /day OR 400 mg × 3 / day

Naproxen

500 mg at onset & 3-5 hours later, then 250 to 500 mg twice /day

Mefenamic acid

500 mg 3times /day



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Medical treatment (AUB-O)

- Metformin

- To restore menstrual cyclicity (30 - 50 ٪)
- To provide endometrial protection (less well established)

➢ When metformin is used, ovulation should be confirmed by :

- The measurement of luteal phase serum progesterone
- Transvaginal ultrasound

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Medical treatment (AUB-O)

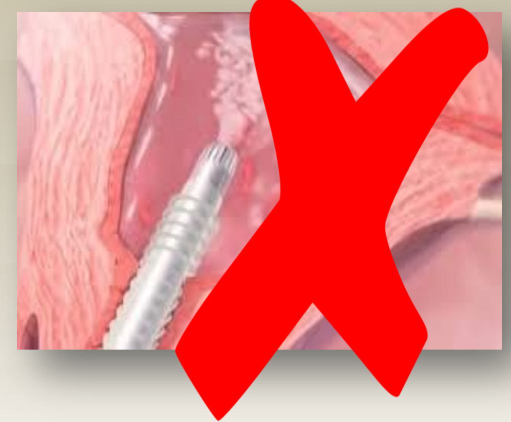
- GnRH agon

- GnRH ant Elagolix)

- Selective rogesterone modulator (Ulipristal)

- ➢ Indicated in bleeding associated with anatomical causes (myoma)
- ➢ **NOT** indicated in AUB-O

Surgical treatment(AUB-O)



Endometrial ablation

- the choice in HMB without desire future pregnancy & considering surgical RX

- Patients with anovulation are at elevated risk for endometrial neoplasia .

- Intrauterine scarring caused by ablation may prevent the cardinal symptom of endometrial neoplasia (bleeding) .

- Conventional approaches to evaluating AUB & endometrial neoplasia (BX & sonohysterogram) may not be feasible following ablation .

Surgical treatment(AUB-O)

The last line ??

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Hirsutism in PCOD

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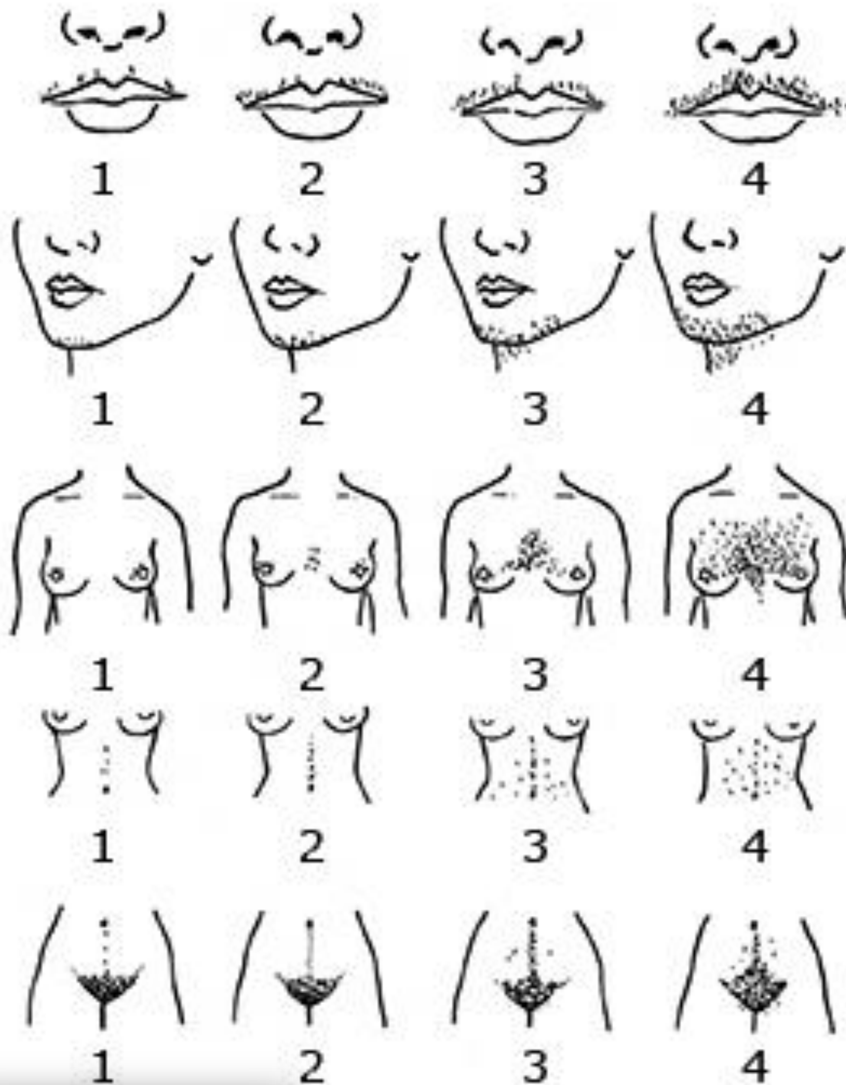
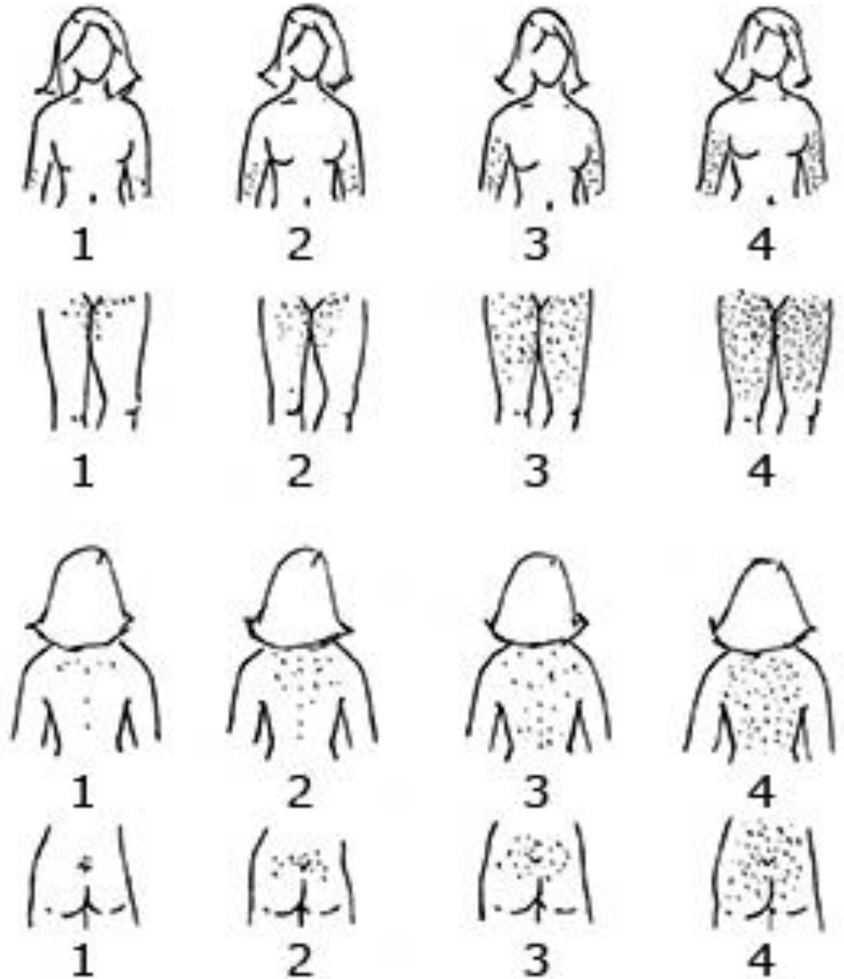
Modified Ferriman-Gallwey score





Definition of Hirsutism

- In the general adult female population a score ≥ 8
- In Asian populations like Chinese as a score ≥ 2 – 3
- In **Mediterranean & Middle East populations** as a score ≥ **9 – 10**

Mild Hirsutism ≥ 8

Moderate & sever Hirsutism > 15

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Indication of Laboratory Evaluation

Laboratory Evaluation is NOT indicated for all women with hirsutism

- primary aim :

Identification of
- serious medical illness
- endocrine disease requiring specific RX

- Non classical CAH
- Androgen secretory tumors
- Cushing disease
- Thyroid diseases
- Hyperprolactinemia

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Indication of Laboratory Evaluation

Laboratory Evaluation is indicated for hirsute women with:

Early morning during follicular phase

- Moderate to sever forms
- Sudden onset
- Rapid progression
- Associated with virilization

Serum total testosterone level :

NL levels = 20-80 ng/dl

Elevated levels > 150 ng/dl

Androgen producing tumors

Rx should be considered in every patient who judges herself hirsute

Serial measurements of serum androgen levels during Rx are not helpful

Repeated hormonal evaluation is indicated when hirsutism progress despite RX

Medical management

1st - line therapy

- **A combined OCP**

- (Endocrine Society Clinical Practice Guidelines on Diagnosis & Treatment of PCOS,2021)

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 6)

- (Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline)

The Journal of Clinical Endocrinology & Metabolism, 2021, on press

- ↓LH dependent ovarian androgen synthesis

-↑ SHBG production

Safe in PCOD patient with / without insulin resistance

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Medical management

1st - line therapy

1st -step

- Start - combined OCPs
- 60-100 % improvement

2nd -step

- In case of suboptimal response , An antiandrogen could be added after 6 months

- In case of bothersome cutaneous manifestations , OCs & an antiandrogen may could be started simultaneously

Medical management

1st - line therapy

Recommendation

- All low dose OCPs (containing 20- 35 mcg of ethinyl estradiol) have similar effectiveness in the RX of hirsutism .

- Start with a preparation containing (20- 35 mcg of ethinyl estradiol) & one of a variety of progestins .

Medical management

1st - line therapy

Recommendation

An OC containing 20 mcg of ethinyl estradiol combined with

- A progestin with minimal androgenicity **(Norgestimate)**
- Other progestins with minimal androgenicity / antiandrogenic properties **(Desogestrel / Drospirenone ,deinogest)**

➢ **Risk of VTE** with newer progestins & drospirenone should be considered .

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Medical management

1st - line therapy

Recommendation

- Start with a new preparations (containing 20 mcg of ethinyl estradiol , 3RD & 4TH generation OCPs) , particularly in association of hirsutism & acne
  (cyproterone acetate , norgestimate, desogestrel, drospirenone)

- Higher doses of ethinyl estradiol are needed in some women for optimal management of hyperandrogenic symptoms.

- **Risk of VTE** with newer progestins & drospirenone should be considered .

Medical management

1st - line therapy

Recommendation

- OCPs should be continued at least for 6 months before judging the effectiveness

- The effective OCP regimen should be continued at least 1-2 years / before attempt for pregnancy

- Permanent hair removal by electrolysis / laser may be required before starting medication / after maximum benefits .

Medical management

1st - line therapy

- **Transdermal / vaginal ring contraceptives :**

Transdermal / vaginal ring preparations are potential options

- **NOT** been well studied for the management of hirsutism
- An **excess** risk of VTE (higher serum estradiol levels)

Medical management

Women with hirsutism & contraindications to Ocs :

Depot medroxyprogesterone acetate

Progesterone only contraceptive

High –dose progestins (MPA 10-20mg/ day)

Appropriate for patients with hirsutism / elevated LH & contraindications to or prefer to avoid estrogen

2nd - line therapy

Medical management

Women with hirsutism & contraindications to Ocs :

-**spironolactone** (50 - 100 mg twice daily)

- An alternative form of contraception is essential .
  (to prevent development of ab normal external genitalia in a male fetus)
- Caution in patient with renal diseases
  (hyperkalemia)

- It alone does not regularize menstrual cycles .
- It is sometimes associated with AUB .
- Progestin therapy is needed .

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2nd - line therapy

Medical management

- **Finasteride** (5 mg / day)

Well tolerated , minimal hepatic toxicity, needs effective contrac

- **Cyproterone acetate** (12.5 – 100 mg)

alone / in combination with estrogen components

- **Flutamide** (250-750 mg/ day)

effective , **NOT** recommend , hepatotoxicity

- **Vaniqa (eflornithine hydrochloride cream 13.9 %)**

NOT a depilatory

Must be used continuously for long period to prevent hair regrowth

appropriate for patient with minimal hair growth

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Medical management

2nd - line therapy

(GnRH) agonists

- for the patients can not tolerate hormonal RX & elevated LH levels

- hormonal RX failure

- Used to suppress ovarian androgen production
  - An "add-back" estrogen-progestin therapy is necessary (to avoid bone loss & estrogen deficiency symptoms)

- Effective

- Limited by its complexity & cost

Medical management

Metformin

- Associated with minimal / no benefit

STATINS

Vitamin D

Inositol

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Medical management

Thanks for
your attention