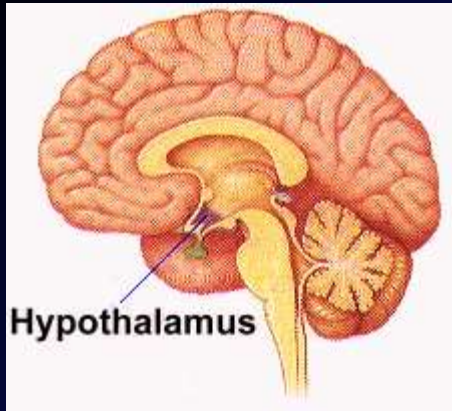


Non hormonal management of midlife bleeding



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Drugs are designed to alter various effects leading to excessive bleeding right from the hypothalamus down to the clot in the menstrual pad.



Medical management

Non Hormonal

NSAID's

Diosmin

Antifibrinolytics:

Tranexamic acid

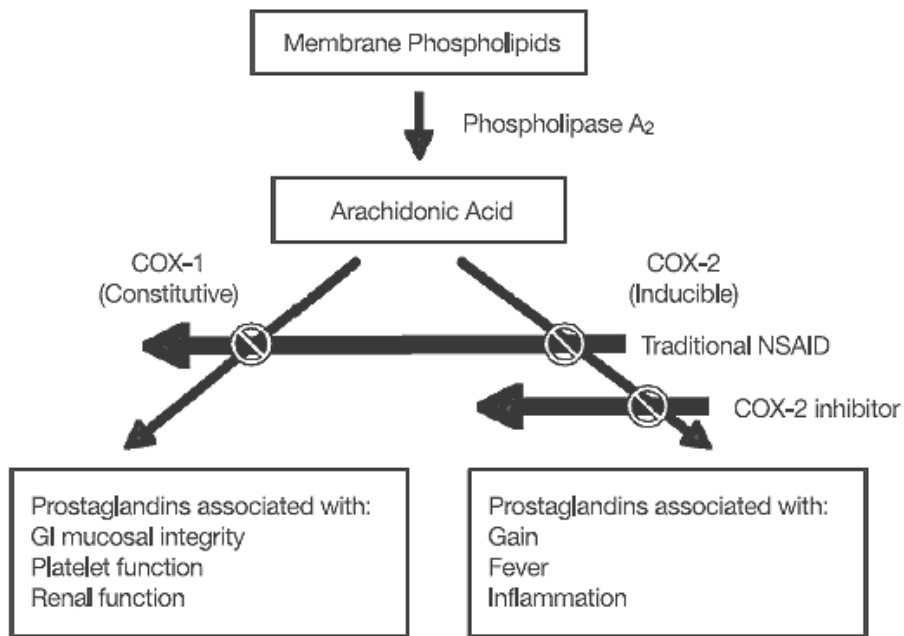
Ethamsylate

Selective Estrogen

Receptor

Modulator:

Ormiloxifene



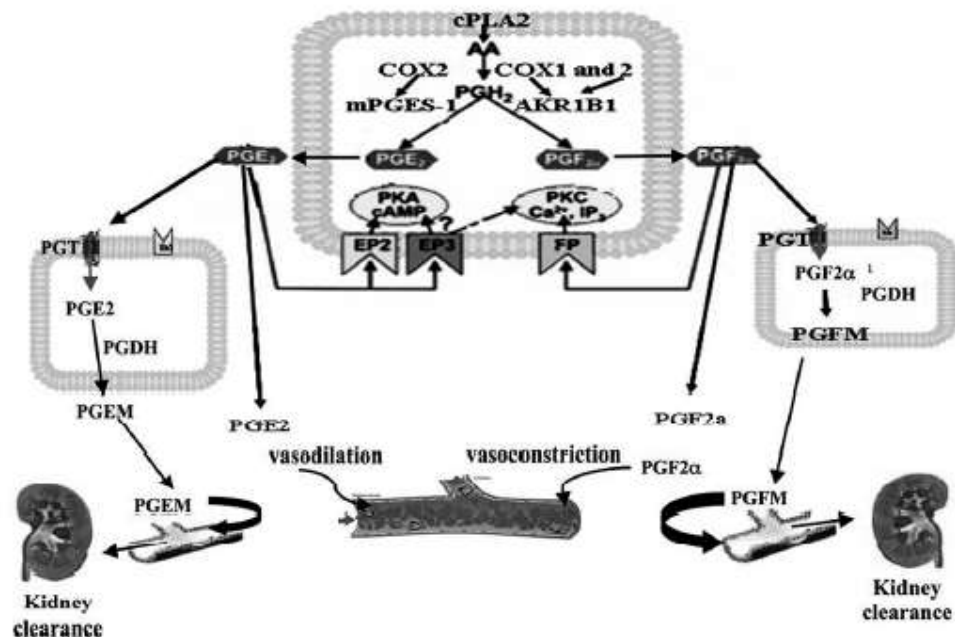
NSAID = nonsteroidal anti-inflammatory drug; COX = cyclooxygenase; GI = gastrointestinal.

Inhibit prostaglandin synthesis:

Endometrial prostaglandins elevated in women with heavy menstrual bleeding.

NSAIDs inhibit cyclo-oxygenase & reduce endometrial prostaglandin levels.

AUTOCRINE AND PARACRINE ACTIONS OF PGE₂ AND PGF₂α IN ENDOMETRIUM



Nonsteroidal antiinflammatory drugs

(decreases flow by 25-40%)

Mefenamic acid 500 mg BiD for 4 -5 days

Naproxen 250 to 500 mg Bid for 4 to 5 d.

Ibuprofen 600 to 1200 mg OD for 4-5 days

James AH, Kouides PA, Abdul-Kadir R, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. [Eur J Obstet Gynecol Reprod Biol 2011;158:124–34.](#)

American College of Obstetricians and Gynecologists. ACOG committee opinion no. 557: management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. [Obstet Gynecol 2013;121\(4\):891–6.](#)



The orange is for more than juice.



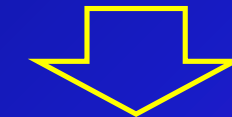
Initially extracted from fig wort in 1925

Diosmin

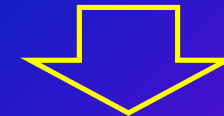
Introduced into therapeutic practice in 1969.



Rinds of citrus fruits



Hesperidin



Diosmin

Diosmin

Diosmin increases the venous tone of the veins and venules and thus improves venous insufficiency and edema of venous origin

► Diosmin also increases the resistance of the capillary walls and normalizes its permeability by restoring the biological integrity of the capillary endothelium.

Diosmin has been shown to suppress prostaglandins E_2 , $F_{2\alpha}$, thromboxane A_2 , and prostacycline;

Reduces capillary hyperfragility; and increases lymphatic drainage

International Journal of Gynecology and Obstetrics (2005) 89, 156—157

G.G. Mukherjeea, **A. J. Gajaraj b**, J. Mathiasc,* , D. Maryad

MPFF was prescribed at a dose of 1000 mg/day (2 tablets of 500 mg)

5 days prior to the expected onset of menstruation (preventive phase)

Up to the end of bleeding (treatment phase)

for three consecutive cycles.

Treatment 5 days prior to and during menstruation reduced menstrual blood flow by one half .

Reduced menstrual duration by one third in about 70% of patients

50% improvement in associated dysmenorrhoea in about three of every four women

1 tablet of 900mg Diosmin would also be good

Table 1 Effect of MPFF treatment at the end of three consecutive menstrual cycles in patients with dysfunctional uterine bleeding manifest as menorrhagia

Parameter	Mean±S.D.		% Change (95% CI)	P value
	Baseline (n=36)	After treatment (n=29)		
PBAC score ^{a,b}	196.9±84.3	94.7±43.2	-51.9 (42.3–75.9)	<0.01
Menstrual flow (days)	8.1±3.1	5.5±1.2	-32.1 (16.7–47.5)	<0.01
Subjective bleeding score ^c	6.4±1.5	2.9±1.4	-54.7 (37.6–71.8)	<0.01
Dysmenorrhoea score ^c	4.9±2.3	2.3±1.8	-53.1 (35.9–70.3)	<0.01
Interference with normal activity score ^c	4.9±1.9	2.3±1.6	-52.1 (34.9–69.3)	<0.01
Satisfaction with treatment score ^{b,c}	2.2±0.7	3.7±0.9	68.2 (52.1–84.3)	<0.01
Haemoglobin (g/dL)	10.0±1.1	10.9±0.9	8.8 (3.1–10.8)	<0.01

^a Pictorial blood assessment chart [3].

^b Value at baseline is the score at the end of first menstrual cycle.

^c On a visual analogue scale (range, 0–10).

Pelvic Venous Congestion

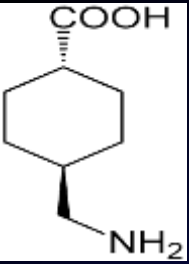
- Varicocities in the pelvic veins could cause pelvic pain
- Patients present with pain during and after intercourse (lasting upto 24 hours)
Backache, dysmenorrhoea
- Pain is more premenstrually , specially while standing.
- On examination there are tender ovaries.
- Pelvic USG study of pelvic veins may be useful
- Laparoscopy is useful

**Diosmin 1000mg per day for 4 months is effective
in treating pelvic venous congestion**

Effect of Daflon on pelvic pain in women with Taylor syndrome:
Talkin O et al., J. Am. Assoc gynaecol Laparosc 3(4Supple) S49, 1996

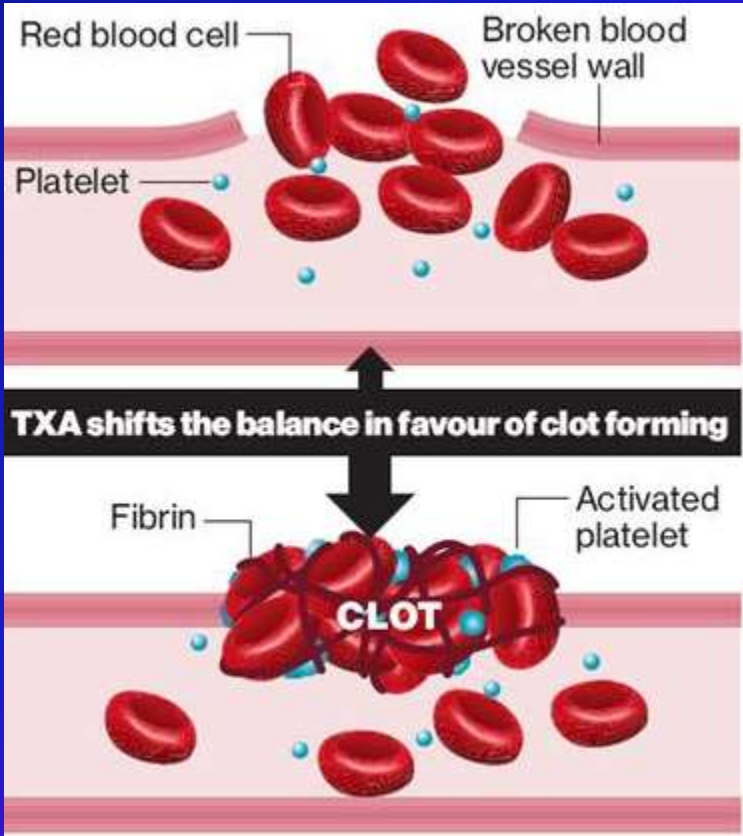
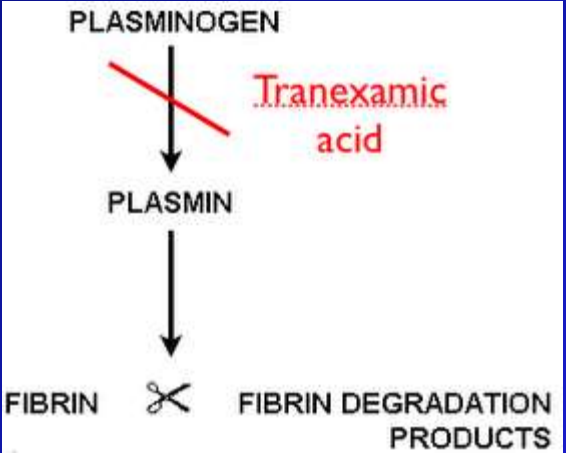
Useful in IUCD bleeding

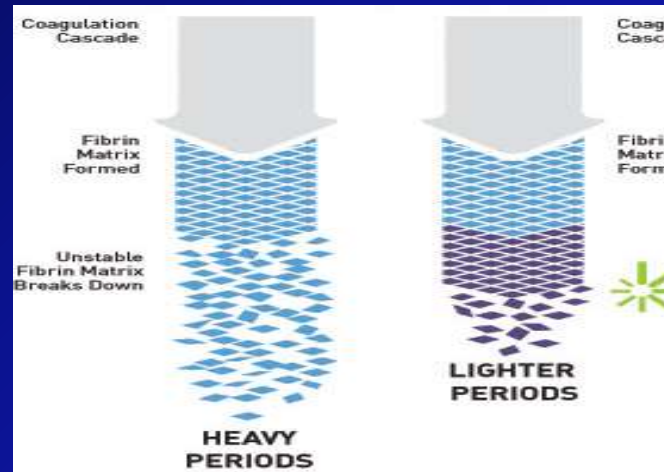
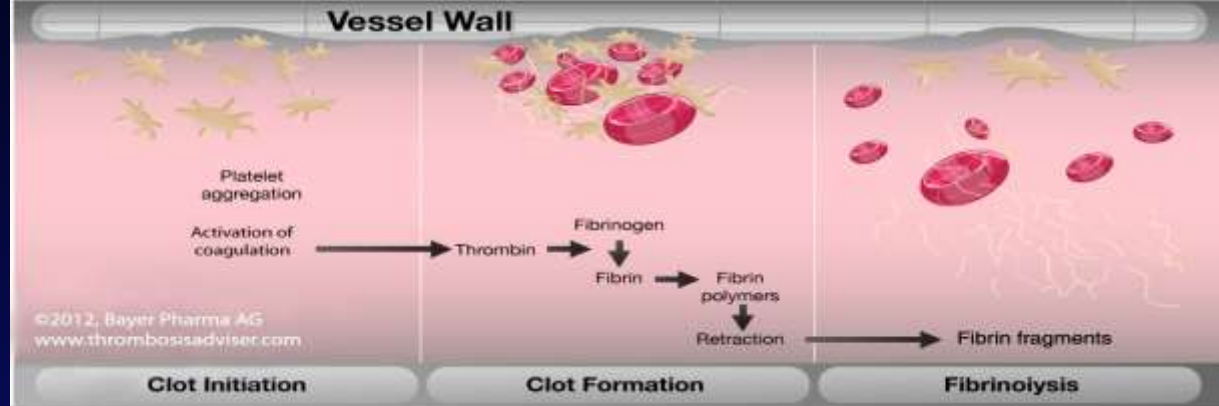
Useful in venous insufficiency of pregnancy



Tranexamic acid

- Prevents plasmin from binding to fibrin, inhibiting fibrinolysis and causes clot formation.
- Reduces menstrual bleeding by 50%.
- Administered from days 1 to 4 or 5 of menses in a dose of 4 g/day.
- Superior to MPA or norethisteron.
- In one study, 3 g/day was also found to be as useful.
- Dose of 2gm/day was just the same as MPA.





Tranexamic acid increases clot formation

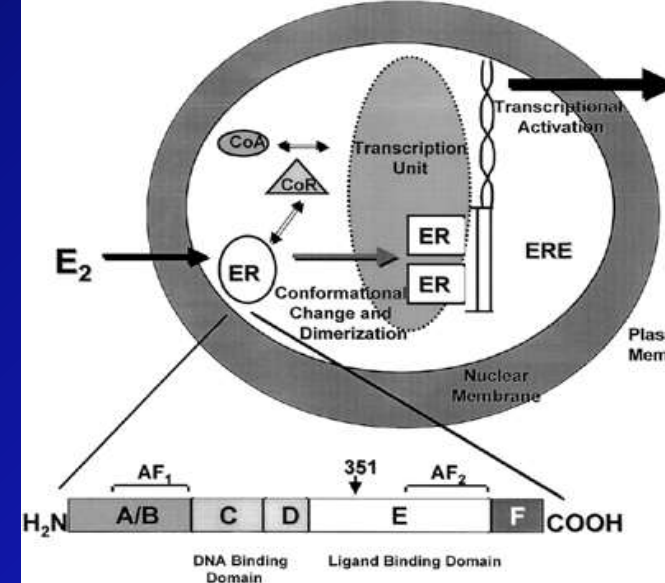
Antifibrinolytics: Tranexamic Acid

**Acute bleeding: 10 mg/kg (IV)
(max 600 mg/dose)**

Ethamsylate

- Ethamsylate is thought to reduce capillary bleeding by correcting abnormal platelet function.
- There is some evidence that it may achieve small reductions in menstrual blood loss, but this is unlikely to be clinically significant [RCOG, 1998; Duckitt, 2000].
- Ethamsylate, at currently recommended doses, is not an effective treatment for menorrhagia (A) [RCOG, 1998].
- It can be used effectively in menorrhagia associated with IUD.

Ormeloxifene : Selective estrogen Receptor modulator



Normalises the bleeding from uterine cavity by blocking the expression of cytosol Estrogen receptors on the endometrium by competitively binding to it.

Prevents proliferation of endometrium.

Ormeloxifene– Dosing Strategy

- Convenient dosage – twice or once weekly
- **60** mg tablet twice a week (for example, Sunday & Wednesday) for 12 weeks followed by one tablet of **60** mg once a week for another 12 weeks

Week 1–12 - 1 tab. Twice Weekly (Day 1 and Day 4)



Week 13–24 - 1 tab. Once Weekly



- **Ormeloxifine has no effect on hypothalmo-pituitary-ovarian axis**
- **Ormeloxifene has no effect on ovulation**

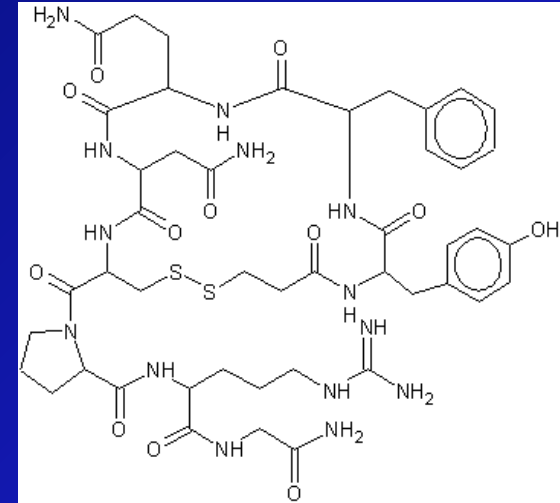
Causes an increase in cycle length by lengthening the follicular phase.

Its contraceptive action is primarily due to the prevention of endometrial decidualization and failure of implantation

- **Ormeloxifene does not cause cystic enlargement of ovaries**
 - It is reported that only 15% patients may develop these, which disappear in subsequent cycles. In the study by Kriplani *et al*, ovarian enlargement was found only in three patients (7.1%)
- **Ormeloxifene does not cause endometrial thickness**
 - In the study by Kriplani *et al*, increased endometrial thickness was found in 9.5% of patients, but there was no atypia on histology. Evaluation of endometrium in one study revealed hyperplasia in only 2.6% of cases and most of the cases had secretory or proliferative or decidual pattern

Desmopressin

- Chemistry : synthetic analogue of vasopressin
- Mechanism of action : Stimulates release of Vwf (von Willibrand factor) from endothelial cells.
- Increases level of factor VIII
- Dose : Highly concentrated nasal spray (1.5mg/ml). (two sprays for the first 2 to 3 days) during menstruation
- Can also be given IV 0.3 microgram/kg diluted in 50ml of normal saline administered over 15-30 minutes



Desmopressin

- Side effects :
 - Facial flushing
 - Headache , blood pressure changes
 - Water retention, hyponataemia
- Efficacy : In adult women without other causes for menorrhagia

Patients receiving anticoagulant treatment
or with a coagulation disorder.

- Multidisciplinary management is recommended.
- Priority for medical treatment: tranexamic acid equally effective as combined estrogen-progestins, and levonorgestrel IUDs
- Specific treatments can be used, such as desmopressin for von Willebrand disease (Grade C).

Conclusion

- Non hormonal therapy for perimenopausal bleeding is safe & effective option.
- All women should be offered primarily with non hormonal treatment in absence of premalignant / malignant pathology.
- If non hormonal therapy fails hormonal therapy or surgical option should be considered.



Thanks