

Management of Urogenital Symptoms in Menopause

陳芳萍 醫師
基隆長庚醫院 婦產科

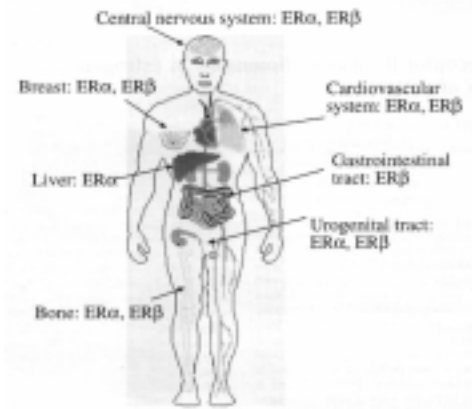
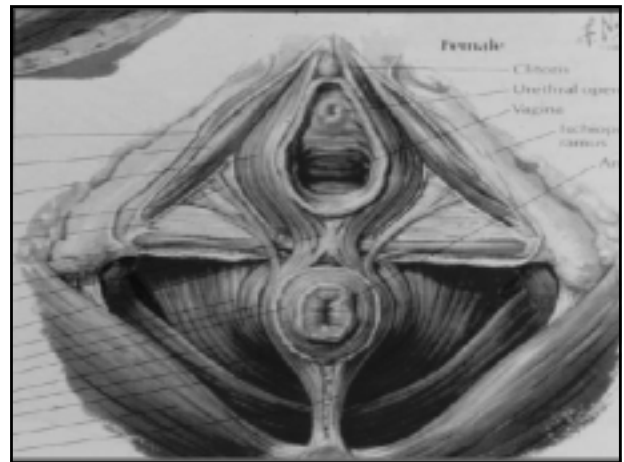
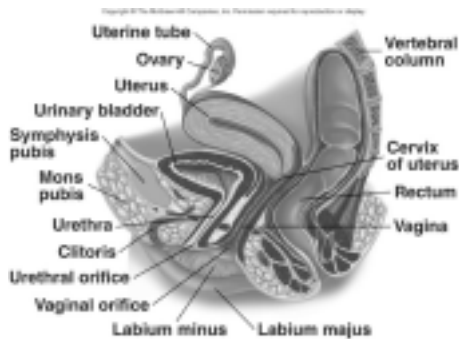
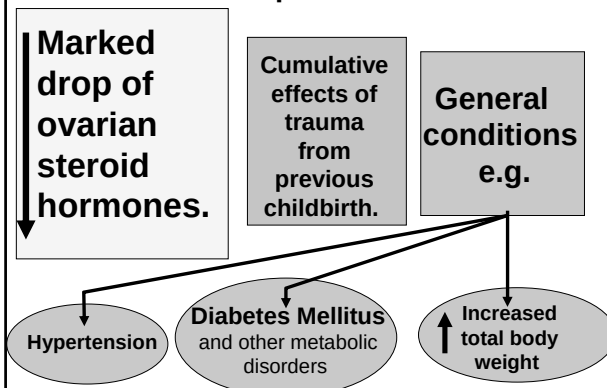


Figure 1 Overall distribution of ERα and ERβ in different tissues.

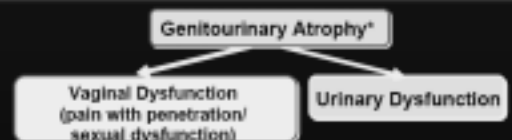
Female Pelvis



Menopause



Genitourinary Changes After Menopause



* Most inevitable, least publicized consequence of estrogen deficiency

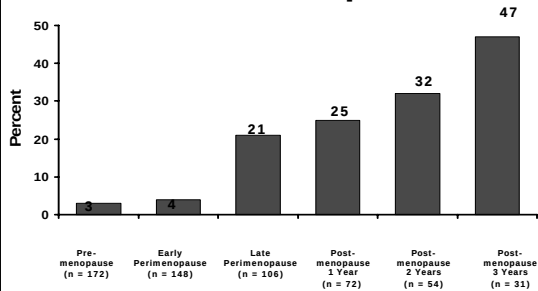
100% of women affected

Up to 45% of elderly women suffer from urinary incontinence

High prevalence of sexual dysfunction in menopause clinics

Weinberger. Clin Obstet Gynecol. 1996;33:175; Sarnet. Obstet Gynecol Clin North Am. 1987;14:48; Gile et al. Obstet Gynecol Surv. 1963;48:508

Increase in Vaginal Dryness With Menopause



Dryness increased significantly in late perimenopause and postmenopause ($P < .001$).
Dennerstein L, et al. *Obstet Gynecol.* 2000;96:351-9.

What Is Senile (Atrophic) Vaginitis?

- An inflammation or irritation of the vagina caused by thinning and shrinking of the tissue of the vagina and decreased lubrication of the vaginal walls.
- This is due to estrogen deficiency.

Presenting Signs and Symptoms

- Genital
 - Dryness
 - Itching
 - Burning
 - Dyspareunia
 - Burning leukorrhea
 - Vulvar pruritus
 - Feeling of pressure
 - Yellow malodorous discharge

Bacteriology (Vaginal Environment)

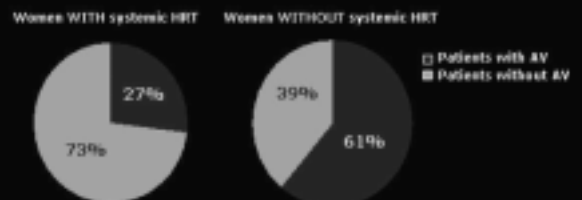
- Vaginal Mucosa Glycogen Diminish
- Intravaginal Lactobacilli Diminish
- pH Rise
- Various Contaminating Organisms Growth
 - Streptococci, Staphylococci (葡萄球菌), Coliform (大腸菌) Bacteria and Diphtheroids (類白喉菌)

Atrophic Vaginitis

- Bacterial infection or tissue reaction to bacterial metabolites
- Bacterial organisms
 - Candidiasis (念珠菌)
 - Trichomoniasis (陰道滴蟲病)
 - Hemophilus (嗜血桿菌) Vaginalis (H. Vaginalis)
 - Streptococci (鏈球菌) (Beta Streptococci and Streptococcus Faecalis)

Epidemiology

Menopausal Women Suffering From Atrophic Vaginitis Physician's Perspective:



Many women using systemic hormone therapy suffer urogenital symptoms

Rotterdam M, et al. *Obstet Gynecol.* 2002;99:956-962

Diagnosis

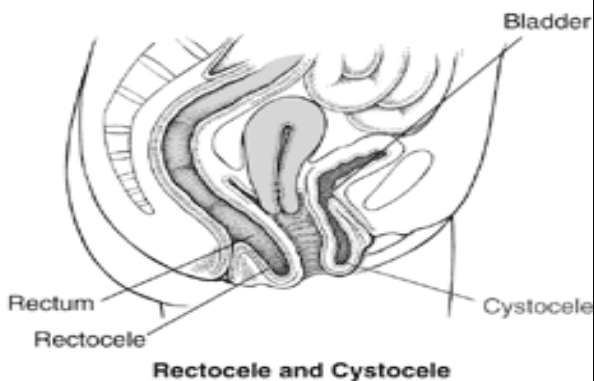
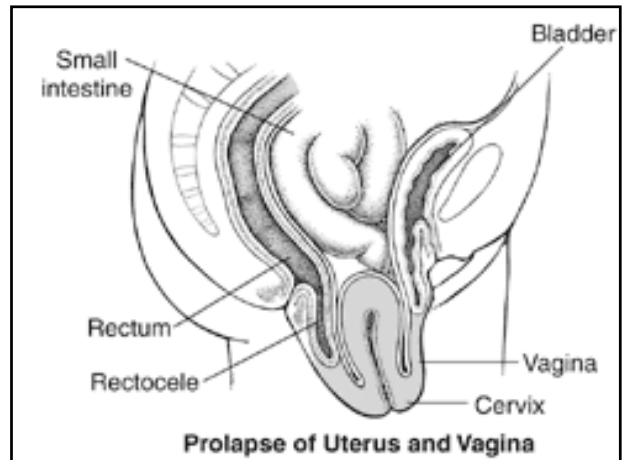
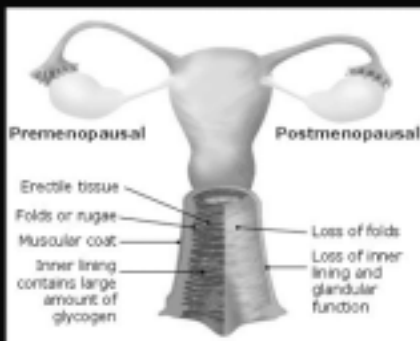
- Physical examination
 - Genital
 - Pale, smooth or shiny vaginal epithelium
 - Loss of elasticity or turgor of skin
 - Sparsity of pubic hair
 - Dryness of labia
 - Fusion of labia minora
 - Introital stenosis
 - Friable, unrugated epithelium
 - Pelvic organ prolapse
 - Rectocele
 - Vulvar dermatoses
 - Vulvar lesions
 - Vulvar patch erythema
 - Petechiae of epithelium
 - Urethral
 - Urethral caruncle
 - Eversion of urethral mucosa
 - Cystocele
 - Urethral polyps
 - Ecchymoses
 - Minor lacerations at peri-introital and posterior fourchette

Atrophy: The Clinical Picture



- 2 years since natural menopause
- No estrogen therapy
 - Loss of labial and vulvar fullness
 - Pallor of urethral and vaginal epithelium
 - Minimal vaginal moisture
 - Loss of urethral meatal turgor

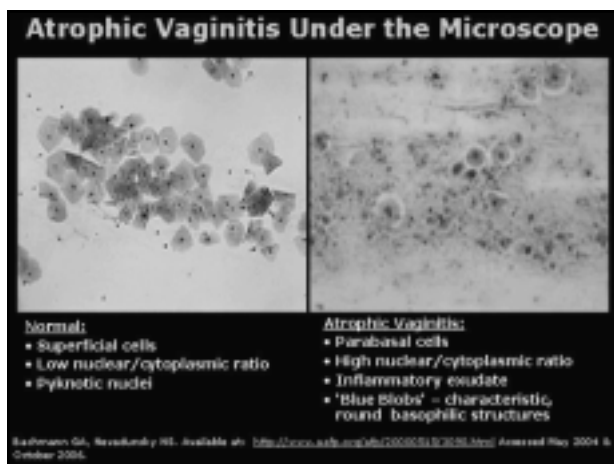
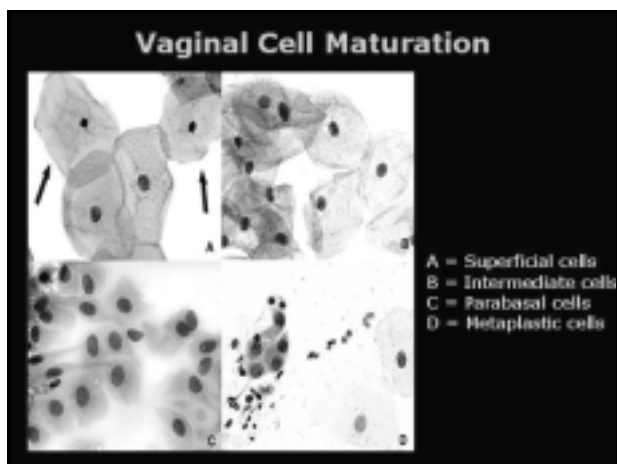
Postmenopausal Changes in the Vaginal Epithelium



Laboratory Diagnosis of Atrophic Vaginitis

Laboratory test

Positive indication



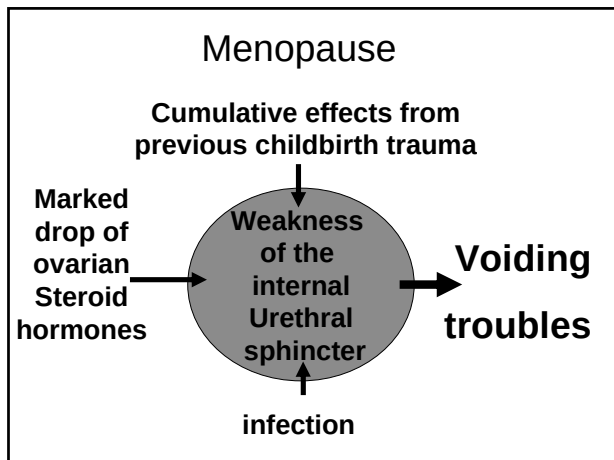
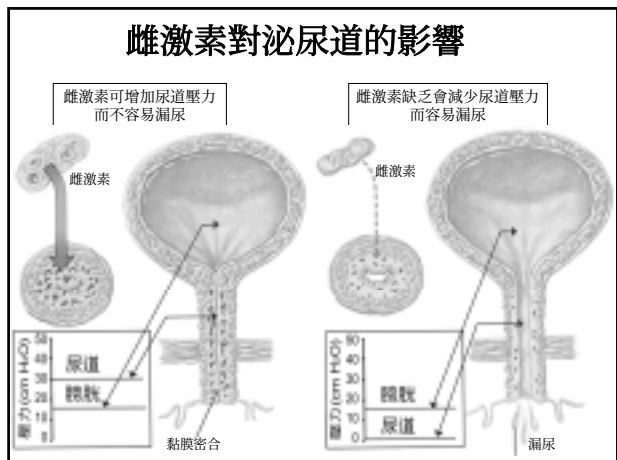
Menopause

- **Marked drop of ovarian steroid hormones will lead to:**
 - loss of urogenital trophic support.
 - atrophy of urogenital tract.
 - atrophy of collagenous tissue of the internal urethral sphincter leading to its weakness
 - atrophy of urothelium, this will increase the chance of infection leading to more persistent, recurrent or chronic infection

Menopause

Estrogen deficiency will lead to drop in the levels of:

- ↓ **Serotonin.** → changes in the mood, and Behavior
- ↓ **Neuro-peptides.**
- ↓ **Nor-epinephrine.** → Decrease of the tone of the int, ureth, sphincter.



● **Collagen atrophy + mucosal thinning in menopause will lead to :**

- Frequency
- Nocturia
- Dysuria
- Urgency
- Cystitis
- SUI
- DI
- Mixed type of incontinence.

Management of urogenital problems in menopause: therapeutic goals

- Relieve symptoms
- Reverse atrophic anatomic changes

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Vaginal atrophy management: treatment options

- Nonhormonal vaginal lubricants and moisturizers are first-line therapy
- Prescription estrogen therapy (ET) may be required for symptomatic vaginal atrophy that does not respond to nonhormonal options

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Treatment of Senile Vaginitis

- Moisturizers and Lubricants
- Estrogen Replacement
- Vitamins: including E and D
- Sexual Activity

Treatment of Senile Vaginitis

—Estrogen Replacement—

- * Systemic administration
 - 10 to 25 % failure rate by standard dosages
 - Up to 24 months of therapy may be necessary to totally eradicate dryness.
- * Local vaginal administration
 - more potent in alleviating symptoms of atrophic vaginitis than oral or transdermal preparation
 - Vaginal Cytology
 - 0.3mg Premarin® Vaginal Cream comparable to 1.25mg Oral Form CEE

HT and Vaginal Atrophy

- When HT is considered solely for this indication, local (not systemic) vaginal ET is generally recommended
- Progestogen generally not indicated with low-dose, local vaginal ET

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Vaginal Estrogen Effects of Various Doses

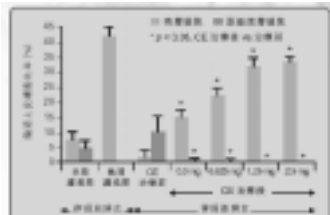
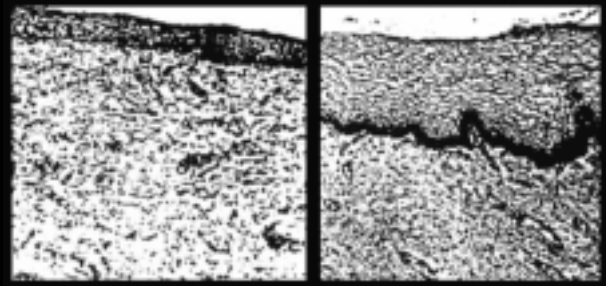


Figure 1: Vaginal Estrogen Effects of Various Doses. The chart shows the percentage of patients with histological improvement for different doses of vaginal estrogen. The Y-axis is labeled 'Percentage of patients with histological improvement' and ranges from 0 to 100. The X-axis shows doses: 0.01mg, 0.02mg, 0.05mg, 0.1mg, 0.2mg, 0.5mg, 1.0mg, and 2.0mg. The data points are approximately: 0.01mg (10%), 0.02mg (15%), 0.05mg (20%), 0.1mg (25%), 0.2mg (30%), 0.5mg (40%), 1.0mg (50%), and 2.0mg (60%). Error bars are shown for each dose.

Reference : J Clin Endocrinol Metab 57: 133-139, 1983

Improvement in Vaginal Histology With Local Estrogen Therapy



Vaginal biopsy showing atrophic changes

The same patient after local estrogen therapy

Courtesy of J. A. E. Nussli, MD.

Benefits of HT in Urinary Problems

- Urinary symptoms:
 - Incontinence –Urethral abnormality, Detrusor instability, Overflow Incontinence
 - Frequency, Urgency, Dysuria
 - Difficulty in voiding
 - Estrogen may produce considerable improvement in these symptoms by increasing
 - Epithelial thickness, vascularity, closing pressure of urethra
 - Adrenergic receptor in bladder urethral muscle
 - Collagen content of connective tissue

Effect of Estrogen Therapy

For recurrent bladder infections:

- Estrogen therapy is more effective than daily antibiotics.
- Topical vaginal estrogen application appears more effective than estrogen by mouth.

Nygard AUGS Quarterly report 1994
Cardozo et al Br J Obstet Gynaecol 1998 vol. 105, 403
Raz et al N Engl J Med 1993 vol. 329, 753

Effect of Estrogen Therapy (8 months of Rx)

Variable	Vag Estrogen (n=50)	Placebo (n=43)
Episodes of bacteria in the urine	12	111
Symptomatic	10	103
Asymptomatic	2	8
UTI per patient/yr	0.5	5.9
No. days antibiotic use	6.9	32

Raz NEJM 1993; 329: 753-756

Evidence Based Medicine

- Topic –
 - “Treatment of atrophic vaginitis with topical conjugated equine estrogens in postmenopausal Asian women”
- Objective –
 - Effects of topical estrogens on atrophic vaginitis and gynecological health in Asian women

Reference: Climacteric 2004; 7: 312-318

Evidence Based Medicine

- Primary outcome – Changes in the vaginal maturation index (VMI)
- Physiological changes assessed by the Genital Health Clinical Examination (GHCE)
 - Vaginal pH, fluid secretion, epithelial mucosa, moisture, rugosity and mucosal color

Evidence Based Medicine

- Multi-center, open-label, 150 postmenopausal women age < 70 years with atrophic vaginitis
 - Taiwan, Hong Kong, Malaysia, Philippines, Singapore and China
 - Vaginal atrophy defined: 0-10% superficial cells or GHCE scored ≤ 15
- 1 G CEE vaginal cream QD at bedtime, on days 1-21 of two 28-day cycles

Evidence Based Medicine

Table 3 Changes from baseline in self-reported vulvovaginal complaints*

Complaint	Baseline	Month 1	p Value vs. baseline	Month 2	p Value vs. baseline
Vaginal dryness	66	19	≤ 0.001	9	≤ 0.001
Vaginal pruritus	5	7	0.124	6	0.336
Vaginal discharge (irritation)	9	7	0.449	6	0.317
Vulvovaginal burning	9	4	0.059	2	0.004
Vulvovaginal itching	30	20	0.018	12	≤ 0.001
Vulvovaginal tenderness	10	6	0.128	3	≤ 0.001
Urinary frequency	31	11	≤ 0.001	7	≤ 0.001
Urinary urgency	16	10	0.029	6	≤ 0.001
Urinary tract infection/burning	8	4	0.083	1	0.003
Painful sexual intercourse (dyspareunia)	24	4	≤ 0.001	1	≤ 0.001
Spotting/bleeding	6	3	0.077	1	0.212

*Values are mean % of days with symptoms.

Evidence Based Medicine

- Result –
 - VMI improved at 1st month, and maintained at 2 months
- Conclusion –
 - Vaginal treatment with CEE cream resulted in beneficial changes in the vaginal tissues and induced an overall genital health pattern more characteristic of the pre-menopausal state.

HT & Self-Reported Urinary Incontinence

- Nurses' Health Study (N = 39,436)
 - Elevated risk of incontinence with HT vs never-users*
 - Risk similar for E alone and E+P
- HERS (N = 2,763)
 - Incontinence improved by 26% with placebo vs 21% with E+P*
- WHI (N = 27,347)
 - E-alone and E+P increased risk among asymptomatic women and worsened symptoms among symptomatic women*

*Did not use urodynamics to assess outcomes.

Grady KL, et al. Obstet Gynecol. 2004;103:344-48.
Grady KL, et al. Obstet Gynecol. 2001;97:115-26.
Hendrix SL, et al. JAMA. 2005;293:935-46.

Efficacy of Low-dose Vaginal Estriol on Urogenital Symptoms

- 88 women with stress incontinence were treated with estriol (n = 44) or placebo (n = 44)
 - Estriol ovule (1 mg) once daily for 2 weeks, then 2 mg once weekly for a total of 6 months
- Vaginal pH, colposcopy, vaginal and urethral smears, and urodynamics were studied
- 68% subjective improvement in incontinence
- Statistical improvement in MUP, MUCP, and PTR

MUP = maximum urethral pressure; MUCP = mean maximum urethral closure; PTR = abdominal pressure transmission ratio.
Gosselin S, et al. Menopause. 2004;11:40-50.

Efficacy of Low-dose Vaginal Estriol on Urogenital Symptoms *continued*

Variables	Treatment Group (n = 44)		Control Group (n = 44)		P-value
	Before Treatment	After Treatment	Before Treatment	After Treatment	
Clinical					
Vaginal dryness	100%	20.5%	100%	99.5%	<.001
Dyspareunia	86.4%	20.5%	84.7%	95.4%	<.001
Urogenital atrophy	100%	27.3%	100%	93.2%	<.01
Urodynamic					
MUP (cm H ₂ O)	50.82 ± 6.15	62.15 ± 8.64	52.35 ± 6.39	49.40 ± 6.54	<.05
MUCP (cm H ₂ O)	45.25 ± 7.20	56.87 ± 9.23	44.77 ± 6.88	43.32 ± 6.32	<.05
PTR (%)	72.52 ± 10.21	88.85 ± 9.66	70.75 ± 9.08	78.77 ± 9.04	<.05

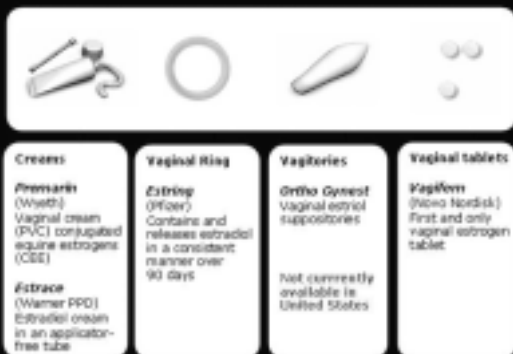
*P-value is comparison between the treatment and control groups. MUP = maximum urethral pressure; MUCP = mean maximum urethral closure; PTR = abdominal pressure transmission ratio.

Adapted from Denstock S, et al. *Menopause*. 2006;11:49-56.

Efficacy of Low-Dose Vaginal Estrogen Preparations

- Vaginal effects are comparable or better than those following systemic HT/ET;
- Long-term effects are better than placebo or nonestrogen treatments;
- Improve symptoms and signs of atrophic vaginitis within 3 weeks in more than 80% of women; and
- Less than 10% of patients experience discharge and/or loss of medication following application.

Atrophic Vaginitis Treatment Options



Choosing vaginal ET

- Low-dose, local, prescription vaginal ET products FDA-approved for treating vaginal atrophy include:
 - estradiol vaginal cream (Estrace Vaginal Cream)
 - CE vaginal cream (Premarin Vaginal Cream)
 - estradiol vaginal ring (Estring)
 - estradiol hemihydrate vaginal tablet (Vagifem)
- All are equally effective at doses recommended in labeling
- Choice depends on clinical experience and patient preference

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Safety of Low-Dose Vaginal Estrogen Preparations

- Low-dose vaginal estrogen preparations induce a small transient increase in plasma 17β-estradiol, but levels remain in the postmenopausal range;
- Vaginal discharge (leukorrhea) is common, and is an expected side effect;
- Long-term treatment may improve bone density, and reduce total serum cholesterol, low-density lipoprotein cholesterol, and apolipoprotein; and
- Low-dose vaginal therapies are unlikely to exert adverse systemic effects, but long-term (> 1 year) risk analysis has not been reported.

Saebagh SA, Smith Agostini M. *Menopause*. 2007;12:626-648.
Kuhl H, Christensen. 2005;6:3-43.

Need for endometrial surveillance

- There are insufficient data to recommend annual endometrial surveillance in asymptomatic women using low-dose, local vaginal ET
- Closer surveillance may be required if a woman is:
 - at high risk for endometrial cancer
 - using a greater dose of vaginal ET
 - having symptoms such as spotting, breakthrough bleeding

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Possible Systemic Effects of Vaginal ET

- Systemic Markers (Such as LH ,FSH and SHBG)
 - 2.5mg Premarin® Vaginal Cream comparable to $\frac{1}{2}$ ~ $\frac{1}{16}$ Oral Form CEE
- Vaginal Cytology
 - 0.3mg Premarin® Vaginal Cream comparable to 1.25mg Oral Form CEE
- Risk of Endometrial Stimulation in long-term treatment ?

Competitor Comparison

產品名稱	Premarin® Vaginal Cream	Ovestin Vaginal Suppository
製造廠	Wyeth	Organon
成份	Conjugated Estrogens	Estriol
劑型	Vaginal Cream	Vaginal Suppository
劑量	0.625mg Conjugated Estrogens / GM	0.5mg/Supp

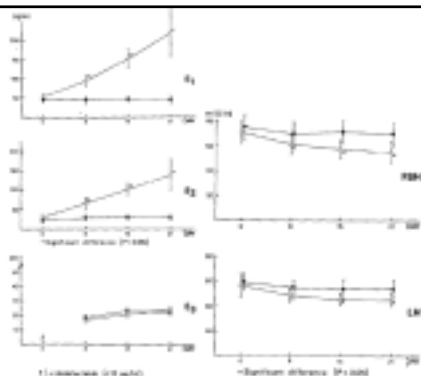


Fig. 1. Mean plasma levels (±SD) of E_1 , E_2 and E_3 in Ovestin (●—●) and Premarin (○—○) treated patients.

Fig. 2. Mean plasma levels (±SD) of FSH and LH in Ovestin (●—●) and Premarin (○—○) treated patients.

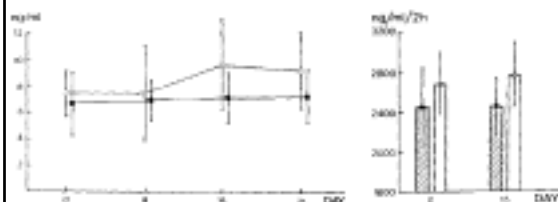
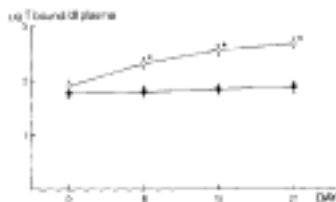


Fig. 3. Mean plasma levels (±SD) and of TRH-stimulated FSH release (right) in Ovestin (●—●) and Premarin (○—○) treated patients.



* Significant difference [P<0.05]
Fig. 4. Mean plasma SHBG capacity (±SD) in Ovestin (●—●) and Premarin (○—○) treated patients.

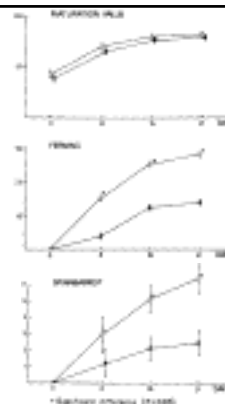


Fig. 5. Mean MV (±SD) in Ovestin (●—●) and Premarin (○—○) treated patients.

Possible Systemic Effects of Vaginal ET

- Preparation containing E1 and/or E2 give rise to unphysiologically high circulating estrogen levels after intravaginal application.
- It possibly leads to unwanted general effects, of which excessive endometrial stimulation is potentially the most dangerous.

Endometrial Risk Assessment: Long-Term Low-Dose Vaginal ET

- Endometrial proliferative changes or an endometrial response to progestin may develop in approximately 5% of women;
- No cases of atypical hyperplasia or endometrial cancer have been reported;
- The estrogen effect on uterine blood flow varies by the vaginal application site:
 - Increased flow when estradiol was applied near the cervix and posterior fornix
 - Few changes were observed when the estrogen was applied to the distal vagina.

Long-term Use of Low-Dose Vaginal ET: Endometrial Protection

- The addition of a progestin to protect the uterus is not necessary when vaginal ET is administered for less than 3–6 months;
- Women with an intact uterus on longer schedules of low-dose vaginal ET should be considered for evaluation of endometrial changes; and
- Meticulous endometrial evaluation should be undertaken in women with:
 - Repeat and marked uterine bleeding
 - Chronic alcohol use
 - Altered liver metabolism

Length of Therapy

- Vaginal ET should be continued as long as distressful symptoms remain

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Conclusions

- Postmenopausal dysfunction of the urogenital organs is unavoidable for all women, although the severity varies among individuals.
- HT combined with pelvic floor physiotherapy and/or surgery is considered useful for improving quality of life in postmenopausal women.

