Management of Urogenital Symptoms in Menopause

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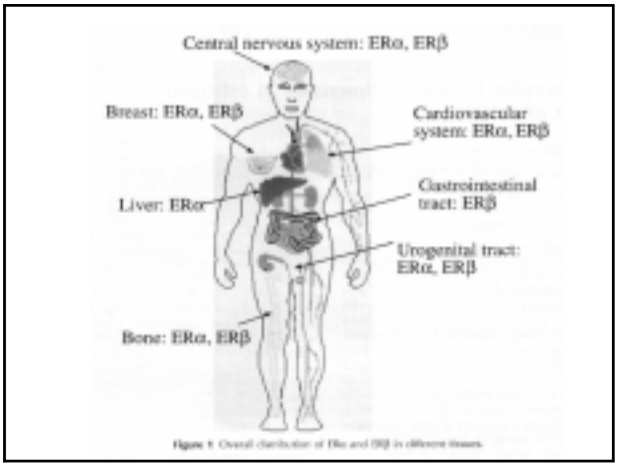
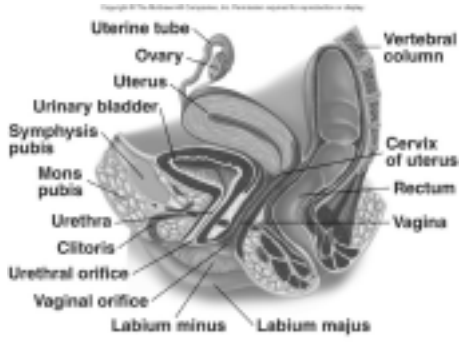
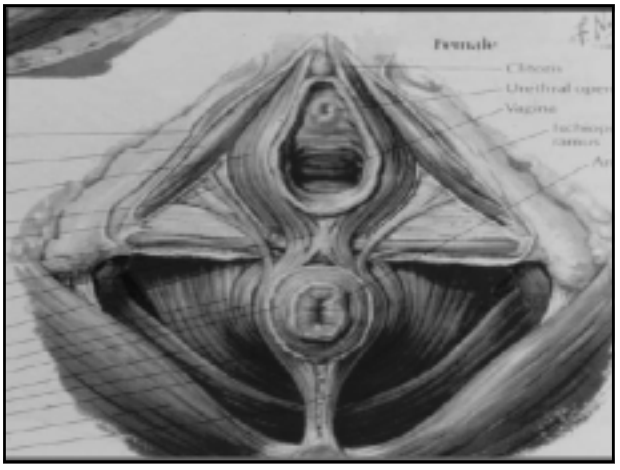


Female Pelvis





Menopause

Marked drop of ovarian steroid hormones.

Cumulative effects of trauma from previous childbirth.

General conditions e.g.

- **Hypertension**
- **Diabetes Mellitus** and other metabolic disorders
- **Increased total body weight**

Genitourinary Changes After Menopause

Genitourinary Atrophy*

- **Vaginal Dysfunction** (pain with penetration/ sexual dysfunction)
- **Urinary Dysfunction**

* Most inevitable, least publicized consequence of estrogen deficiency

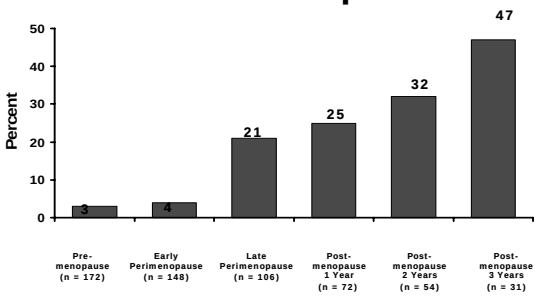
100% of women affected

Up to 45% of elderly women suffer from urinary incontinence

High prevalence of sexual dysfunction in menopause clinics

Weinberger, Clin Obstet Gynecol. 1996;39:17; Sarrel. Obstet Gynecol Clin North Am. 1987;14:49; Ella et al. Obstet Gynecol Surv. 1993;48:509.

Increase in Vaginal Dryness With Menopause



Dryness increased significantly in late perimenopause and postmenopause ($P < .001$).
Dennerstein L, et al. *Obstet Gynecol.* 2000;96:351-8.

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

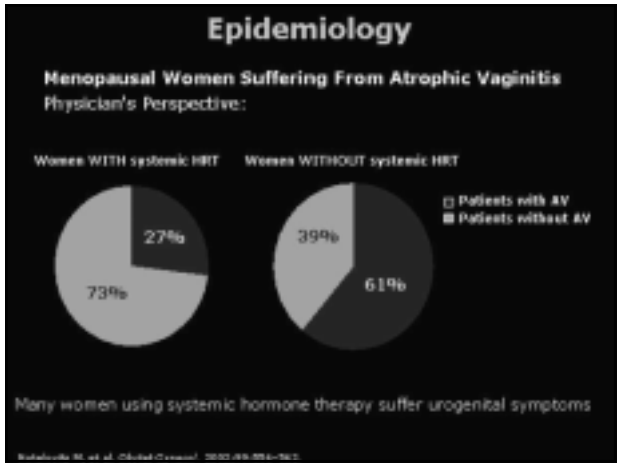
- Genital
  - Dryness
  - Itching
  - Burning
  - Dyspareunia
  - Burning leukorrhea
  - Vulvar pruritus
  - Feeling of pressure
  - Yellow malodorous discharge

Bacteriology (Vaginal Environment)

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

Atrophic Vaginitis

- Bacterial infection or tissue reaction to bacterial metabolities
- 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)

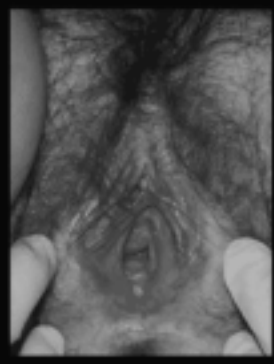


Diagnosis

- 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

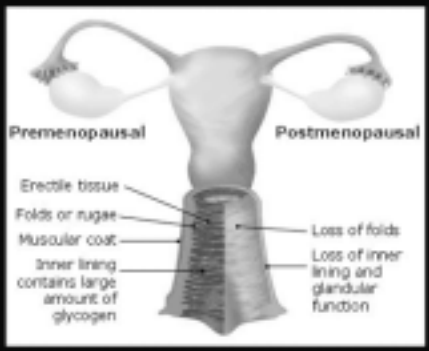
  Urethral
  - Urethral caruncle
    Eversion of urethral mucosa
    Cystocele
    Urethral polyps
    Ecchymoses
    Minor lacerations at peri-introital and posterior fourchette

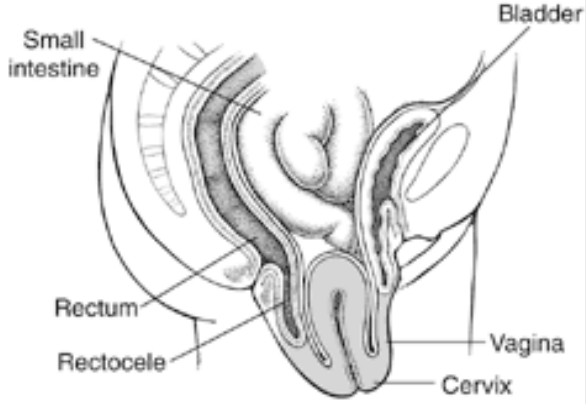
Atrophy: The Clinical Picture



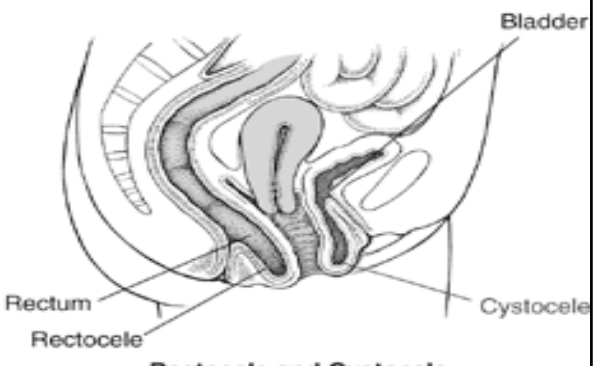
- 2 years since natural menopause
- No estrogen therapy
  - Loss of labial and vulvar fullness
  - Pallor of urethral and vaginal epithelium
  - Minimal vaginal moisture
  - Loss of urethral meatal turgor

Postmenopausal Changes in the Vaginal Epithelium





Prolapse of Uterus and Vagina

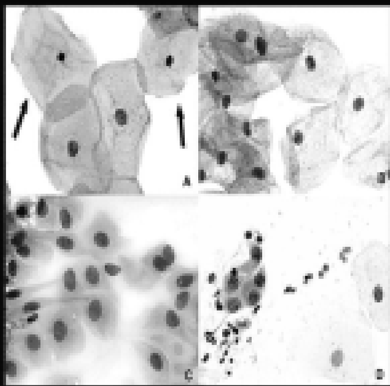


Rectocele and Cystocele

Laboratory Diagnosis of Atrophic Vaginitis

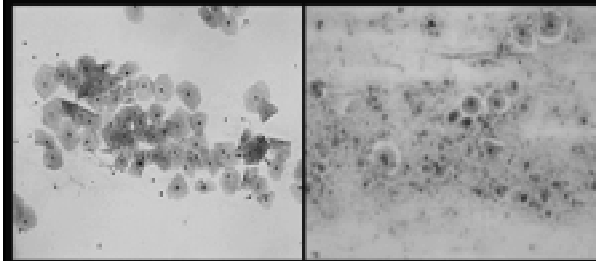
Laboratory test	Positive indication

Vaginal Cell Maturation



A = Superficial cells
B = Intermediate cells
C = Parabasal cells
D = Metaplastic cells

Atrophic Vaginitis Under the Microscope



Normal:
- Superficial cells
- Low nuclear/cytoplasmic ratio
- Pyknotic nuclei

Atrophic Vaginitis:
- Parabasal cells
- High nuclear/cytoplasmic ratio
- Inflammatory exudate
- 'Blue Blobs' – characteristic, round basophilic structures

Bachmann GA, Nevadunsky NS. Available at: [illegible] Accessed May 2004 & October 2006.

Menopause

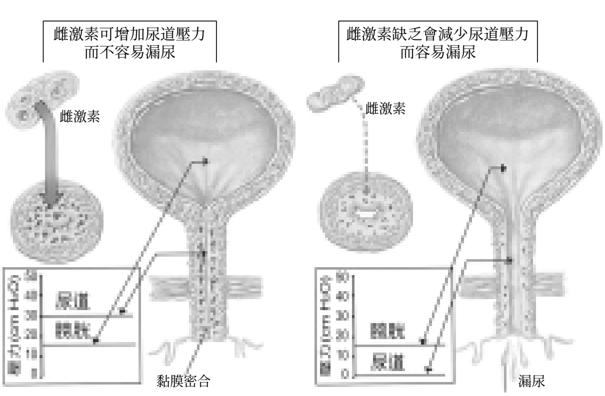
- **Marked drop of ovarian steroid hormones will lead to:**
  - **loss of urogenital trophic support.**
  - **atrophy of urogenital tract.**
  - **atrophy of collagenous tissue of the internal urethral sphincter leading to its weakness**
  - **atrophy of urothelium, this will increase the chance of infection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

Menopause

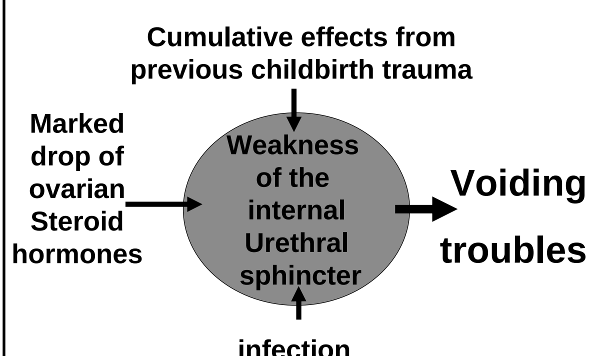
Estrogen deficiency will lead to drop in the levels of:

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

雌激素對泌尿道的影響



Menopause



- ***Collagen atrophy + mucosal thinning in menopuase 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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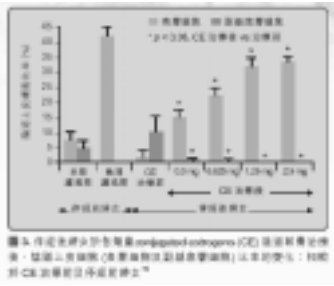
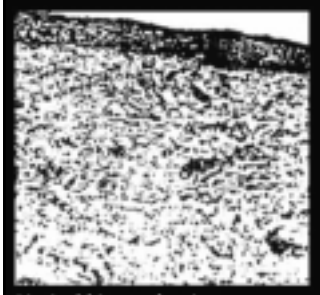
Vaginal Estrogen Effects of Various Doses

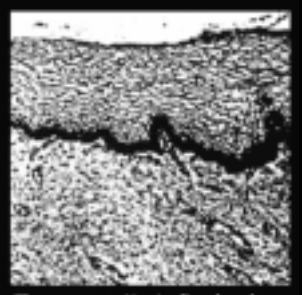


Reference : *J Clin Endocrinol Metab* 57: 133-139, 1983

Improvement in Vaginal Histology With Local Estrogen Therapy



Vaginal biopsy showing atrophic changes



The same patient after local estrogen therapy

Benefits of HT in Urinary Problems

- Urinary symptoms:
  - Incontinence –Urethral abnormality, Detrussor 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.

Nygaard AUGS Quarterly report 1994
Cardozo et al Br J Obstet Gynecol 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

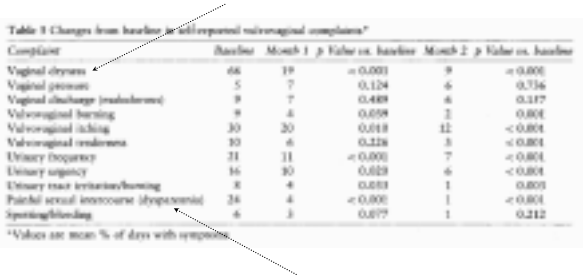


Table 3 Changes from baseline in self-reported vulvovaginal complaints*

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	0.736
Vaginal discharge (malodorous)	9	7	0.489	6	0.317
Vulvovaginal burning	9	4	0.059	2	0.001
Vulvovaginal itching	30	20	0.018	12	< 0.001
Vulvovaginal tenderness	10	6	0.228	3	< 0.001
Urinary frequency	21	11	< 0.001	7	< 0.001
Urinary urgency	16	10	0.029	6	< 0.001
Urinary tract irritation/burning	8	4	0.053	1	0.003
Painful sexual intercourse (dyspareunia)	24	4	< 0.000	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.

Grodstein F, et al. Obstet Gynecol. 2004;103:254-60.
Grady D, et al. Obstet Gynecol. 2001;97:116-20.
Hendrix SL, et al. JAMA. 2005;293:935-48.

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.
Ozerdogan N, et al. Menopause. 2004;11:49-56.

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

Variables	Treatment Group (n = 44) Before Treatment	Treatment Group (n = 44) After Treatment	Control Group (n = 44) Before Treatment	Control Group (n = 44) After Treatment	P-Value*
Clinical					
Vaginal dryness	100%	20.5%	100%	90.9%	<.001
Dyspareunia	86.4%	20.5%	84.1%	86.4%	<.001
Urogenital atrophy	100%	27.3%	100%	93.2%	<.01
Urodynamic					
MUP (cm H_2O)	50.82 ± 6.15	62.15 ± 8.64	52.35 ± 6.30	48.40 ± 6.54	<.05
MUCP (cm H_2O)	45.25 ± 7.20	56.87 ± 9.23	44.77 ± 6.88	43.32 ± 6.32	<.05
PTR (%)	72.52 ± 10.31	88.85 ± 9.66	70.75 ± 9.08	70.77 ± 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 Dessole S, et al. Menopause. 2004;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

Creams

Premarin (Wyeth) Vaginal cream (PVC) conjugated equine estrogens (CEE)

Estrace (Warner PPD) Estradiol cream in an applicator-free tube

Vaginal Ring

Estring (Pfizer) Contains and releases estradiol in a consistent manner over 90 days

Vagitories

Ortho Gynest Vaginal estriol suppositories

Not currently available in United States

Vaginal tablets

Vagifem (Novo Nordisk) First and only vaginal estrogen tablet

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

NAMS position statement. *Menopause* 2007.

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.

Gallagh SA. *Semin Reprod Med.* 2005;23:126-143.
Kuhl H. *Climacteric.* 2005;8:3-63.

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 ½ ~ 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**

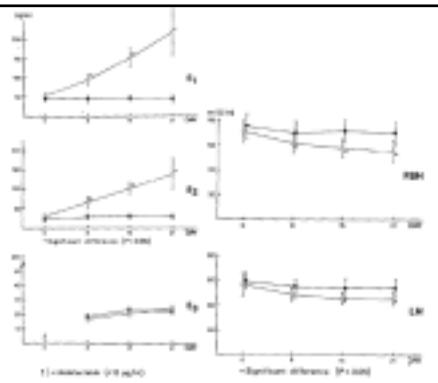

Fig. 1. Mean plasma levels (±SD) of E_1, E_2 and E_3 in Ovestin (●——●) and Premarin (○——○) treated patients.

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

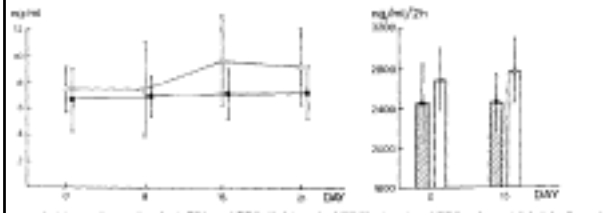

Fig. 3. Mean plasma levels (±SD) and of TRH-stimulated PRL release (right) in Ovestin (●——●) and Premarin (○——○) treated patients.

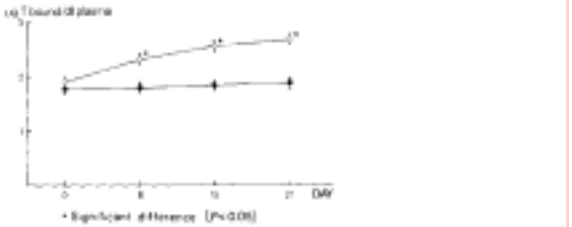

Fig. 4. Mean plasma SHBG capacity (±SD) in Ovestin (●——●) and Premarin (○——○) treated patients.

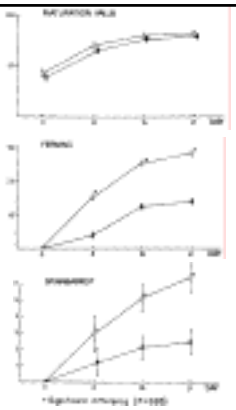

Fig. 5. Mean MV (±SD) in Ovestin (●——●) and Premarin (○——○) treated patients.

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

NAMS position statement. *Menopause* 2007.

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.