

일반의와 간호사를 위한 강좌

# ▶ 무월경과 부정출혈의 호르몬 치료법 ▶

이화의대 정경아



# 무월경



- (Novak) Primary amenorrhea
  - : Absence of menses at **age 13 years** + no visible development of secondary sexual characteristics
  - : **Age 15 years** in the presence of normal secondary sexual characteristic
- (Speroff)
  - : No menses by age 14 in the absence of growth or development of secondary sexual characteristics
  - : No menses by age 16 regardless of the presence of normal growth and development of secondary sexual characteristics
  - : No menses for an interval of time equivalent to a total of **at least three previous cycles, or 6 months**

# 부정출혈



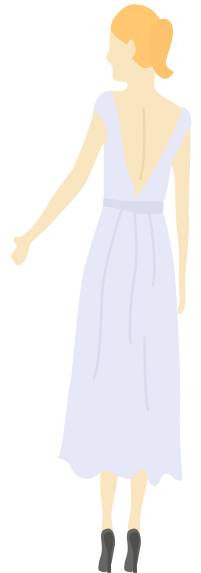
- Abnormal uterine bleeding (formerly, dysfunctional uterine bleeding)
- Irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy
- It reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining
- The bleeding is unpredictable: excessively heavy or light and may be prolonged, frequent, or random
- About 1-2% of women with improperly managed anovulatory bleeding eventually may develop endometrial cancer



# 호르몬 치료법



- Progesterone
- Estrogen
- OC



# Bioassays of Estrogen Production

- **Progestin challenge test**

- **Endometrial thickness**

: In one study involving 44 women with secondary amenorrhea, endometrial thickness was significantly greater in 32 women who had withdrawal bleeding ( $10.3 \pm 4.1$  mm) than in 12 who did not ( $5.0 \pm 1.3$  mm)

: The serum E2 level also was significantly greater ( $45.3 \pm 19.4$  vs.  $18.6 \pm 8.0$  pg/mL), and an **endometrial thickness measuring 6mm or greater** predicted withdrawal bleeding with 95% accuracy

# Estrogen/Progesterone

- Physiologic levels of estrogen can be achieved using oral (micronized estradiol 1–2 mg daily or conjugated equine estrogens 0.625–1.25 mg daily) or transdermal treatment regimens (0.1 mg/24 hours)
- Intact uterus: cyclic or continuous treatment with a progestogen is essential to prevent endometrial hyperplasia and neoplasia that can result from treatment with estrogen alone
- Cyclic treatment with a progestogen (micronized progesterone 200 mg daily or medroxyprogesterone acetate 10 mg daily for 12–14 days each month) is preferable for those still hoping to conceive

# OC

- Oral contraceptives contain substantially greater amounts of hormones
- To prevent even the possibility of random ovulation and pregnancy
- Ethinyl estradiol 0.02mg or 0.03mg+drospirenone 3mg/  
desogestrel 0.15mg/levonorgestrel 0.15mg/gestodene 0.075mg

# OC/Postmenopausal HT

- It is important to change because even with the lowest estrogen dose oral contraceptive available, the estrogen dose is 4-fold greater than the standard post-menopausal dose
- With increasing age, the dose-related risks with estrogen become significant
- Beginning at age 50, on an annual basis, being careful to obtain the blood sample on day 6 or 7 of the pill-free week in a standard regimen (when steroid levels have declined sufficiently to allow FSH to rise)
- When FSH is greater than 20 IU/L, it is time to change to a postmenopausal hormone program



# Risks and benefits of HT

- It is important to emphasize to young women that they are distinctly different from older postmenopausal women
- The balance between the risks and benefits of hormone therapy for them also differs from that in postmenopausal women
- Because they are significantly younger, their baseline risks for cardiovascular disease and breast cancer are much lower than those for older postmenopausal women
- Without estrogen therapy, their risk for later coronary heart disease may be increased, rather than decreased
- Hormone therapy should continue up to at least age of 50, in much the same way as endogenous hormone production does in normal women

# Hormone therapy might be underutilized in women with early menopause

L. Lindh-Åstrand<sup>1</sup>, M. Hoffmann<sup>2</sup>, L. Järvstråt<sup>3</sup>, M. Fredriksson<sup>3</sup>,  
M. Hammar<sup>1</sup>, and A.-C. Spetz Holm<sup>1,\*</sup>

**STUDY QUESTION:** Are Swedish women age 40–44 years with assumed early menopause ‘undertreated’ by hormone therapy (HT)?

**SUMMARY ANSWER:** Many women with probable early menopause discontinue their HT after a short period of time. Thus, they fail to complete the recommended replacement up to age 51–52 years, the average age of menopause.

**WHAT IS KNOWN ALREADY:** Spontaneous early menopause occurs in ~5% of women age 40–45 years. Regardless of the cause, women who experience hormonal menopause due to bilateral oophorectomy before the median age of spontaneous menopause are at increased risk of cardiovascular disease, neurological disease, osteoporosis, psychiatric illness and even death.

**STUDY DESIGN, SIZE, DURATION:** The study is descriptive, and epidemiological and was based on the use of national registers of dispensed drug prescriptions (HT) linking registers from the National Board of Health and Welfare and Statistics Sweden from 1 July 2005 until 31 December 2011.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** The study population consisted of 310 404 women, 40–44 years old on 31 December 2005 who were followed from 1 July 2005 until 31 December 2011.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Only 0.9% of women 40–44 years old started HT during the study period. A majority of these women used HT <1 year.

**LIMITATIONS, REASONS FOR CAUTION:** We do not know the indications that led to the prescription of HT but assume that early onset of menopause was the main reason. Because of the study design—making a retrospective study of registers—we can only speculate on the reasons for most of the women in this group discontinuing HT. Another limitation of this study is that we have a rather short observation time. However, we have up to now only been able to collect and combine the data since July 2005.

**WIDER IMPLICATIONS OF THE FINDINGS:** As the occurrence of spontaneous early menopause in women age 40–45 is reported to be ~5%, the fact that <1% of Swedish women age 40–44 are prescribed HT, and can be shown also to have had the medication dispensed at a pharmacy suggests an unexpectedly low treatment rate. Some women with early menopause may have used combined contraceptives as supplementation therapy, but in Sweden HT is the recommended treatment for early menopause so any such women are not following this recommendation. Women who experience early menopause are at increased risk for overall morbidity and mortality, and can expect to benefit from HT until they have reached at least the median age of spontaneous menopause. It is therefore important to individualize the information given these women and to convey new knowledge in this area to gynaecologists and physicians in general as well as the recommendation that women in this group continue HT at least until the average age for spontaneous menopause is reached.

## GENERAL GYNECOLOGY

# Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States, 2003–2008

Ekwutosi M. Okoroh, MD; W. Craig Hooper, PhD; Hani K. Atrash, MD; Hussain R. Yusuf, MD; Sheree L. Boulet, DrPH

**OBJECTIVE:** We sought to determine prevalence and likelihood of venous thromboembolism (VTE) among women with and without polycystic ovary syndrome (PCOS).

**STUDY DESIGN:** We performed a cross-sectional analysis using Thomson Reuters MarketScan Commercial databases for the years 2003 through 2008. The association between VTE and PCOS among women aged 18–45 years was assessed using age-stratified multivariable logistic regression models.

**RESULTS:** Prevalence of VTE per 100,000 was 374.2 for PCOS women and 193.8 for women without PCOS. Compared with women without PCOS, those with PCOS were more likely to have VTE (adjusted odds

ratio [aOR] 18–24 years, 3.26; 95% confidence interval [CI], 2.61–4.08; aOR 25–34 years, 2.39; 95% CI, 2.12–2.70; aOR 35–45 years, 2.05; 95% CI, 1.84–2.38). A protective association (odds ratio, 0.8; 95% CI, 0.73–0.98) with oral contraceptive use was noted for PCOS women.

**CONCLUSION:** PCOS might be a predisposing condition for VTE, particularly among women aged 18–24 years. Oral contraceptive use might be protective.

**Key words:** polycystic ovary syndrome, prevalence, venous thromboembolism

Cite this article as: Okoroh EM, Hooper WC, Atrash HK, et al. Is polycystic ovary syndrome another risk factor for venous thromboembolism? United States, 2003–2008. Am J Obstet Gynecol 2012;207:377.e1–8.

# Treatment of AUB

- The primary objective of treatment in women with anovulatory bleeding is to induce or restore the natural control mechanisms that are not operating: synchronous growth, development, and shedding of a structurally **stable endometrium**
- **Hospitalization** is indicated for women with active hemorrhage who are hemodynamically unstable and those with symptomatic anemia or a serious underlying medical illness
- The best choice in a given patient depends primarily on the condition of the endometrium: It is important to emphasize that progestin treatment is unlikely to be effective in patients with a thin, attenuated, or denuded endometrium
- **Transvaginal ultrasonography** should be performed before treatment begins, to identify any obvious pathology that may dictate management and to assess the endometrial thickness

# Progestin therapy

- In oligomenorrheic anovulatory women with episodic abnormal bleeding: predictable, self-limited progestogen withdrawal bleeding can be induced by cyclic treatment with an orally active progestin (medroxyprogesterone acetate 5–10 mg daily for 12–14 days each month)
- Failed progestin treatment suggests strongly that other pathology is causing or contributing to the problem and signals the need for additional diagnostic evaluation
- Although cyclic progestin therapy generally works well in women who are completely anovulatory and not sexually active, treatment with an estrogen-progestin contraceptive is the better choice for those who likely still ovulate (albeit infrequently) or want to avoid pregnancy

# Progestin therapy

- Standard cyclic progestin treatment regimens do not reliably suppress the hypothalamic-pituitary-ovarian axis, will not prevent random ovulation, and are not contraceptive
- If not warned to expect the heavy menses and increased dysmenorrhea likely to arrive within 2–4 days after treatment stops, most women will interpret the experience as more of the same and treatment failure

# Progesterone injection

- 슈게스트 주: progesterone 100mg/2ml
- 근육 주사
- 용법 · 용량:
  - 무월경; 월경주기 후반 2주 동안 1회 25mg 주 3회 주사
  - 부정출혈; 월경예정일 시작 2일 전까지 5일 동안 1일 5-10mg 주사
  - 월경곤란증, 월경전증후군; 월경 시작 전 1주간 10-25mg 매일 주사

# Progestin therapy

- Depot-medroxyprogesterone acetate(every 3 months) can be a useful option for maintenance therapy in women who have difficulty with or cannot take estrogen-progestin contraceptives
- Depot progestin treatment has no place in the acute management of abnormal bleeding: Once given, it cannot be withdrawn, and if unsuccessful, its effects can be difficult to overcome; Episodic breakthrough bleeding is relatively common and can be treated with estrogen



# Depot-MPA injection

- 주성분: medroxyprogesterone acetate 104mg/0.65mL suspension for injection
- 효능 · 효과: **피임, 자궁내막증**으로 인한 통증 관리
- 용법 · 용량: 매 3개월 (12-14주)마다 앞쪽 넓적다리 또는 복부에 **피하주사**, **체중에 따른 용량 조절이 필요 없음**, 균일한 현탁액을 만들기 위해 프리필드시린지를 사용 직전에 세계 흔들어야 함



# Biological Activities of Progestogens

Biological activities of natural progesterone and synthetic progestins

Progestin	Progesto- genic	Anti-gonado- tropic	Anti- estrogenic	Estro- genic	Andro- genic	Anti-andro- genic	Gluco- corticoid	Anti- mineralo- corticoid	
Progesterone	+	+	+	—	—	±	+	+	
Dydrogesterone	+	—	+	—	—	±	—	±	듀파스톤
Medrogestone	+	+	+	—	—	±	—	—	
17 $\alpha$ -Hydroxy-derivatives									
Chlormadinone acetate	+	+	+	—	—	+	+	—	
Cyproterone acetate	+	+	+	—	—	++	+	—	
Megestrol acetate	+	+	+	—	±	+	+	—	
Medroxy-progesterone-acetate	+	+	+	—	±	—	+	—	프로베라
19-Nor-progesterone-derivatives									
Nomegestrol acetate	+	+	+	—	—	±	—	—	
Promegestone	+	+	+	—	—	—	—	—	
Trimegestone	+	+	+	—	—	±	—	±	
Spirolactone-derivatives									
Drospirenone	+	+	+	—	—	+	—	+	야스민 야즈
19-Nortestosterone derivatives									
Norethisterone	+	+	+	+	+	—	—	—	
Lynestrenol	+	+	+	+	+	—	—	—	
Norethinodrel	±	+	±	+	±	—	—	—	
Levonorgestrel	+	+	+	—	+	—	—	—	미니보라 미레나
Norgestimate	+	+	+	—	+	—	—	—	
3-Keto-desogestrel	+	+	+	—	+	—	—	—	
Gestoden	+	+	+	—	+	—	+	+	마이보라
Dienogest	+	+	±	±	—	+	—	—	클레라

Taken from reference [5,7,8,10–15]. (+) effective; (±) weakly effective; (—) not effective.

# Estrogen-Progestin therapy

- Women with anovulatory bleeding who are sexually active and not immediately prepared to pursue pregnancy generally are best managed by treatment with an estrogen-progestin contraceptive
- Acute prolonged episodes of heavy anovulatory bleeding also can be treated effectively with high-dose estrogen-progestin therapy, provided that the endometrium is normal or increased in thickness
- Any **monophasic combination oral contraceptive** can be used, beginning with one pill twice daily, and decreasing to one pill daily thereafter

# Estrogen-Progestin therapy

- Treatment should continue for a total of at least 2 weeks, even when bleeding markedly slows or stops, which generally can be expected within 24–48 hours
- Unexplained menorrhagia: estrogen-progestin contraceptives can be expected to decrease bleeding by up to 40%
- Failed estrogen-progestin indicates the need for additional diagnostic evaluation



## CLINICAL ARTICLE

## A national survey of gynecologists on current practice patterns for management of abnormal uterine bleeding in South Korea

Ji Young Lee <sup>a,1</sup>, Dong-Yun Lee <sup>b,1</sup>, Jae Yen Song <sup>c</sup>, Eun Sil Lee <sup>d</sup>, Kyungah Jeong <sup>e</sup>, DooSeok Choi <sup>b,\*</sup><sup>a</sup> Department of Obstetrics and Gynecology, Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, South Korea<sup>b</sup> Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea<sup>c</sup> Department of Obstetrics and Gynecology, Uijeongbu St. Mary's Hospital, Catholic University of Korea, Uijeongbu-si, South Korea<sup>d</sup> Department of Obstetrics and Gynecology, Soonchunhyang University Seoul Hospital, Soonchunhyang University School of Medicine, Seoul, South Korea<sup>e</sup> Department of Obstetrics and Gynecology, Ewha Womans University, Seoul, South Korea

## ARTICLE INFO

## Article history:

Received 27 November 2014

Received in revised form 1 April 2015

Accepted 8 June 2015

## Keywords:

Abnormal uterine bleeding

Clinician survey

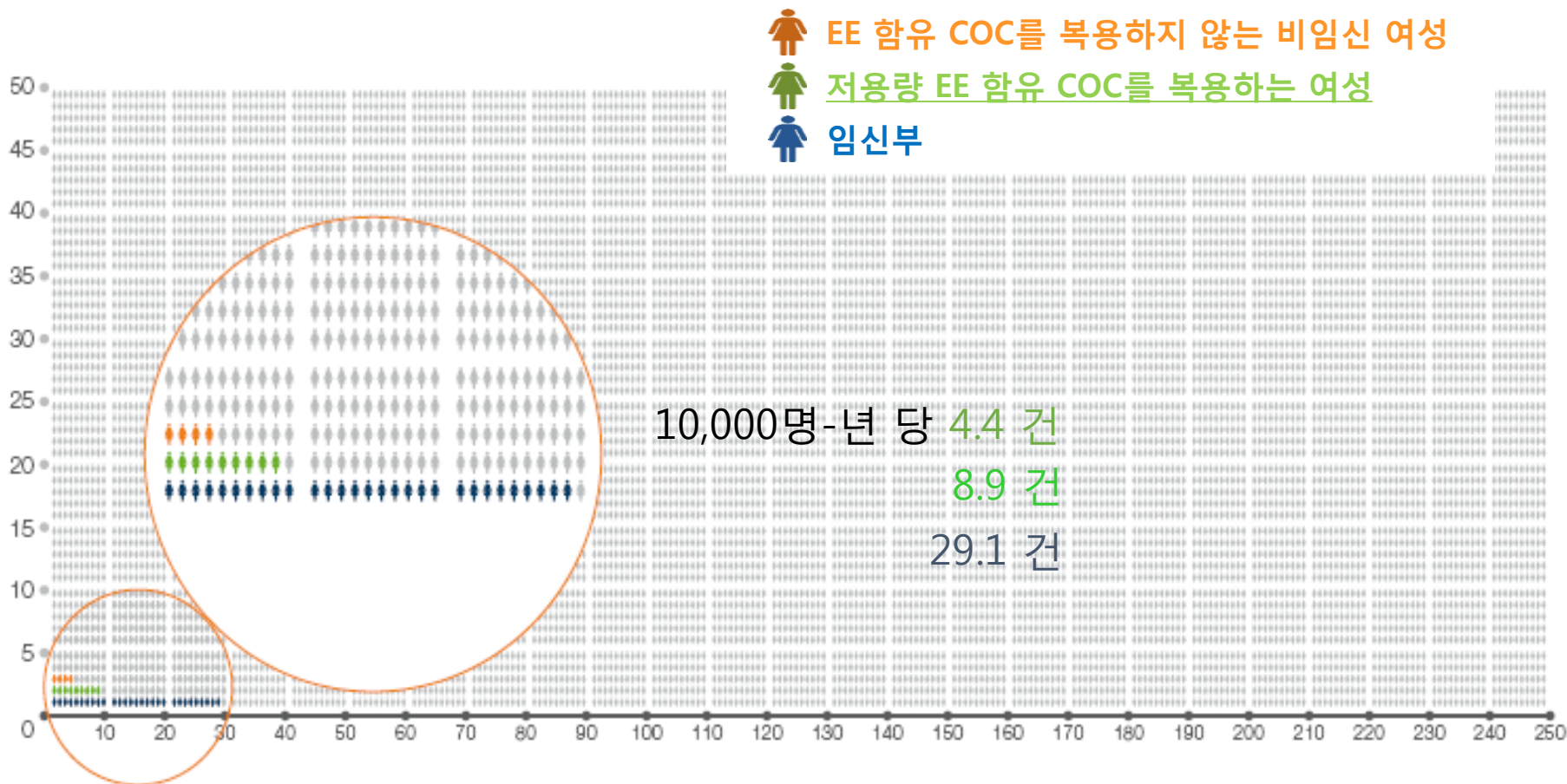
Management

## ABSTRACT

**Objective:** To evaluate practice patterns of gynecologists in the management of abnormal uterine bleeding (AUB) in South Korea. **Methods:** Between February 24 and March 12, 2014, a cross-sectional survey was performed through face-to-face interviews with 100 gynecologists selected through quota sampling reflecting regions and hospital types. Through the use of a questionnaire, the level of awareness and practice patterns regarding diagnosis and management of AUB were evaluated. **Results:** Among 100 respondents, 60 reported that they had not previously heard of the International Federation of Gynecology and Obstetrics (FIGO) classification system. The standardization of AUB terminology was reported to be necessary or very necessary by 70 respondents. Pelvic ultrasonography would be used for diagnosis by 99 physicians. The most common first-line AUB treatment was combined oral contraceptives: 55 respondents would use them for heavy menstrual bleeding, 56 for intermenstrual bleeding, and 56 for polycystic ovary syndrome. Combined oral contraceptives were the preferred follow-up medication: 30 would use them for heavy menstrual bleeding, 24 for intermenstrual bleeding, and 52 for polycystic ovary syndrome. **Conclusion:** Despite implementation of the FIGO AUB classification system and guidelines, awareness and use among gynecologists in South Korea remains low.

© 2015 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd. All rights reserved.

# VTE 발생률



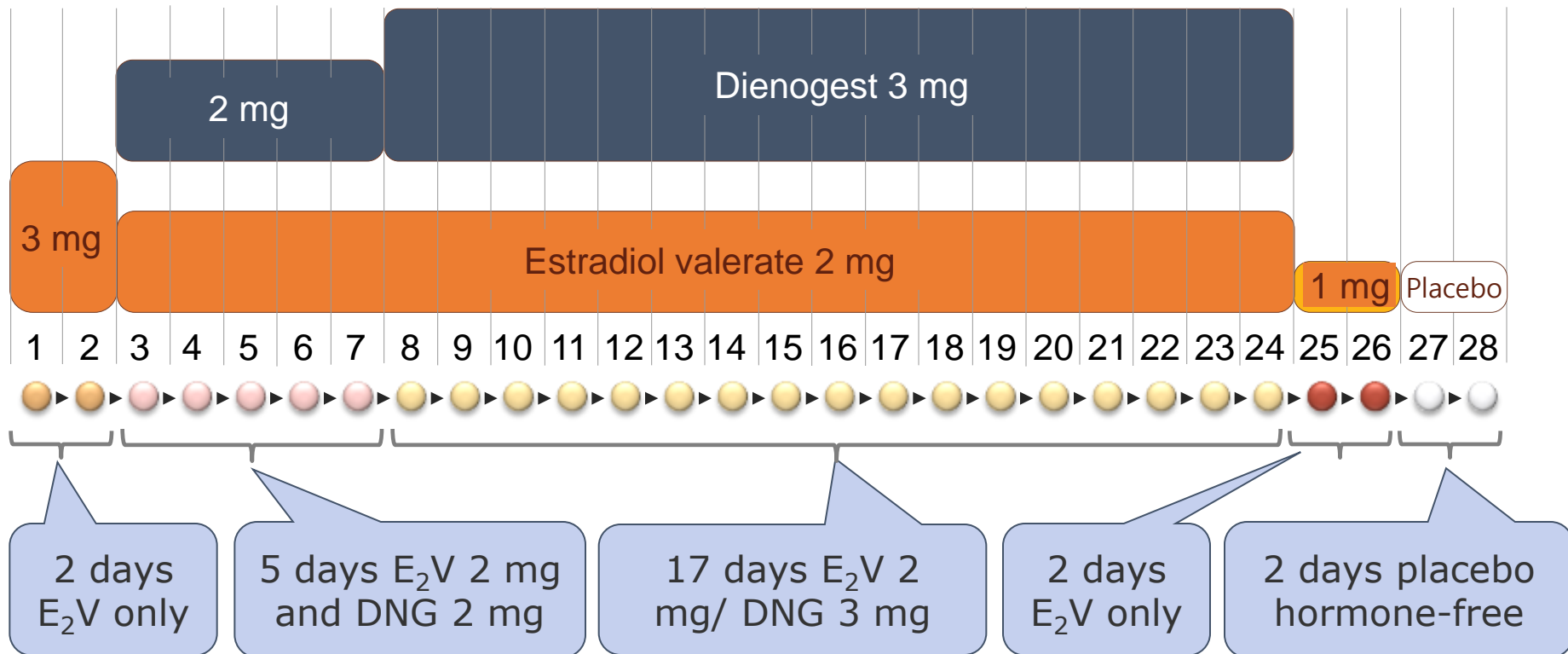
\*10,000인-년 당  
 EE: Ethinyl estradiol  
 Dinger et al. Contraception 2007;75(5):344-54



# Dynamic Dosing with Qlaira®



- 26 active tablets – estrogen step-down, progestogen step-up



# Qlaira®

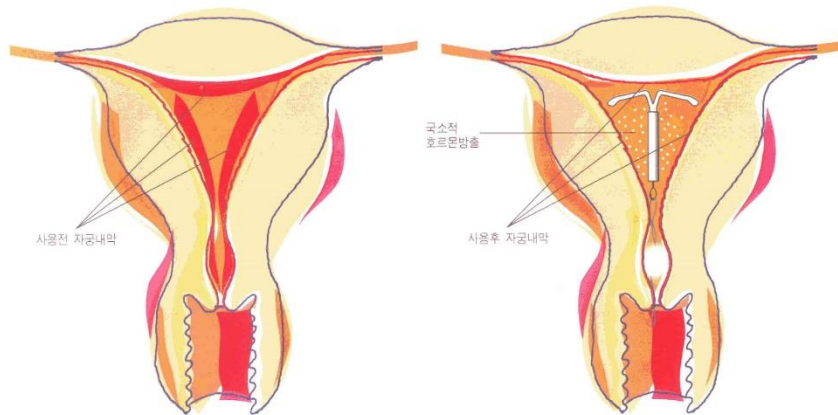
- Natural estrogens such as estradiol (E2) or its valerate ester
- E2V offer an alternative to ethinyl estradiol(EE)
- E2-containing combined oral contraceptives (COCs) have demonstrated sufficient ovulation inhibition and acceptable contraceptive efficacy
- The E2V/DNG combination provides early estrogenic dominance to ensure initial endometrial proliferation and endometrial stroma stability during the progestogen-dominated mid-to-late part of the cycle
- DNG has potent endometrial activity and a bioavailability of >90% after oral intake
- Effective for the treatment of heavy menstrual bleeding(HMB)

(Gynecological Endocrinology 2012;28(5):400–8)



# LNG-IUS

- Menstrual blood loss in women with heavy menstrual bleeding can be reduced by 75–95%, due to progestin-induced decidualization of the endometrium
- The LNG-IUS is an attractive option for ovulatory women with heavy menstrual bleeding and for women with intractable bleeding associated with chronic illnesses (renal failure)
- Levonorgestrel 52mg/set, 20 $\mu$ g/day



# Estrogen therapy

- When acute, heavy bleeding results in a thin, denuded endometrium, high-dose estrogen therapy is the best initial treatment; progestin or estrogen-progestin therapy is unlikely to succeed and may aggravate the problem
- In patients who are hemodynamically unstable, intravenous estrogen therapy (25mg conjugated equine estrogens every 4 hours intravenously until bleeding subsides, for up to 24 hours) is very effective
- High-dose intravenous or oral estrogen treatment may increase the risk of thromboembolism: There are no data that quantify the risk, but venous and pulmonary embolism are a potential complication and have been reported
- As with any therapeutic decision, the benefits of treatment must be weighed against its potential risks and those of alternative methods for the management of abnormal uterine bleeding: In women with a past episode or family history of thromboembolism, high-dose estrogen treatment should be avoided

# Estrogen injection

- 프레마린 주: conjugated estrogen 25mg
- 용법 · 용량: 1회 20-25mg을 천천히 정맥 또는 근육 주사
- 필요한 경우, 6-12시간 후에 반복 투여

# Management of Oncological risk

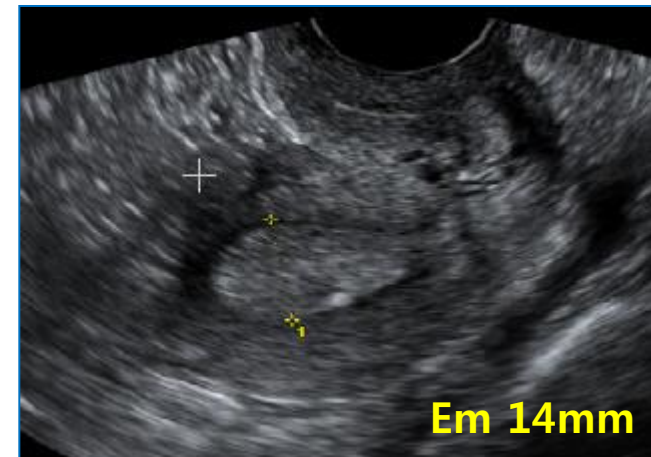
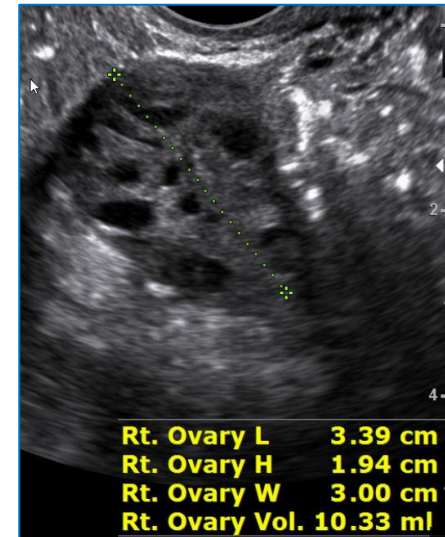
Clinical assessment	Therapeutic approaches
<p>In presence of amenorrhoeic patients or abnormal uterine bleeding,</p> <p>assessment for the presence of endometrial cancer</p> <p>with ultrasound and/or endometrial biopsy</p>	<p><b>Periodic progestogen withdrawal (at least four episodes per year)</b></p> <p>should be indicated</p> <p>in anovulatory PCOS women</p>



# Case 1

- G0P0, 26세, 14세 menarche 후 계속 irregular menstruation, AUB, **local PG injection**
- 161cm, 46kg, BMI 17.7kg/m<sup>2</sup>, BP 100/68 mmHg
- TSH 1.71 uIU/ml, PRL 8.9 ng/ml  
E2 49 pg/mL, FSH 4.8 mIU/ml, LH 10.3 mIU/ml  
TT 54, cal fT 0.931 ng/dL
- TC 197-LDL 110-HDL 77-TG 89 mg/dL
- FBS 96 mg/dL, HbA1c 5.1%

→ Complex hyperplasia with atypia

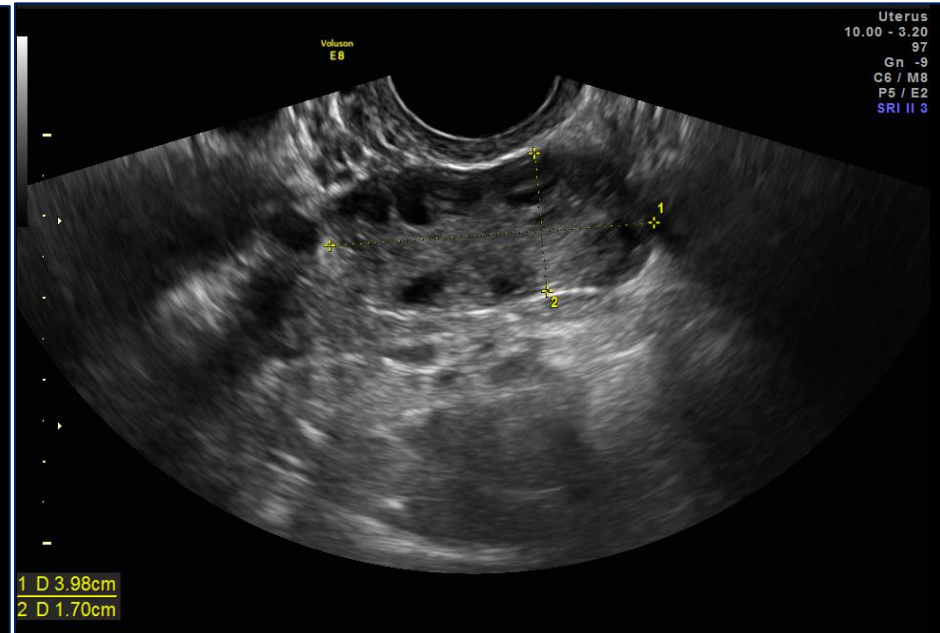
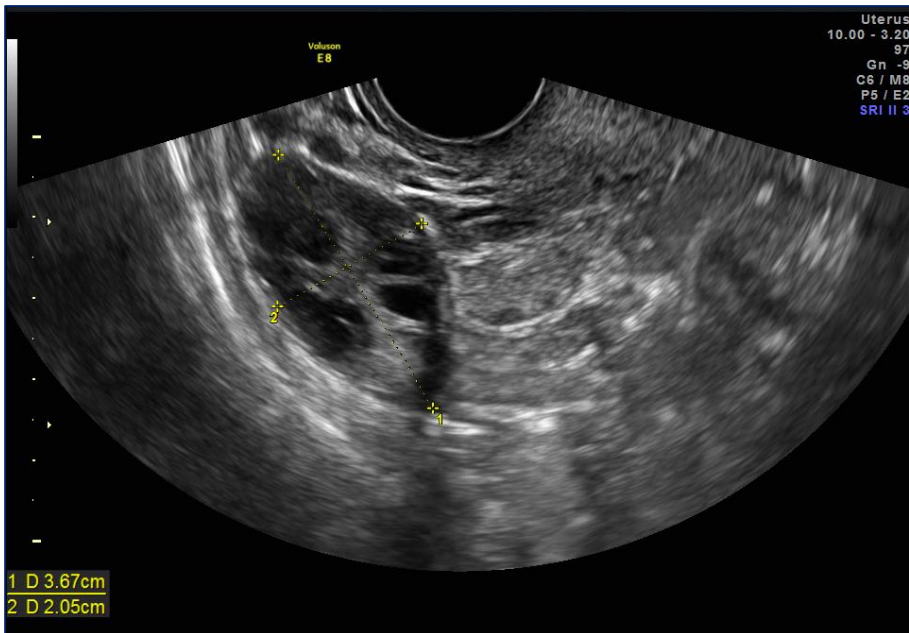
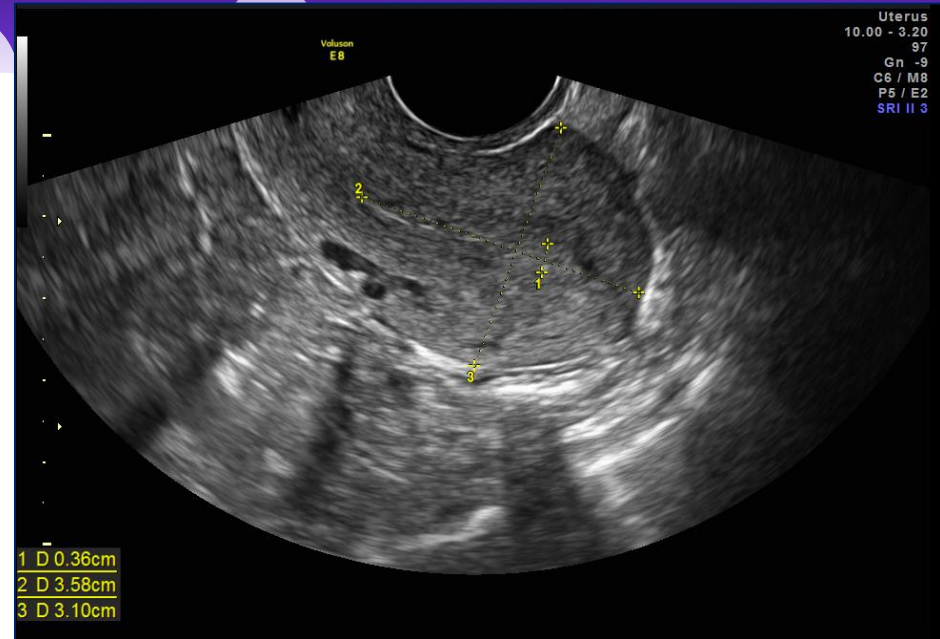




## Case 2

- 25세, Amenorrhea, 10kg 감량
- TSH 0.78  $\mu$ U/mL, PRL 6.2 ng/mL
- E2 46 pg/mL
- FSH 5.6 mIU/mL, LH 21.7 mIU/mL
- TT 77 ng/dL, cal fT 1.08 ng/dL

→ **E+P** tx







Thank you!!