PCOS in Middle-Aged Women

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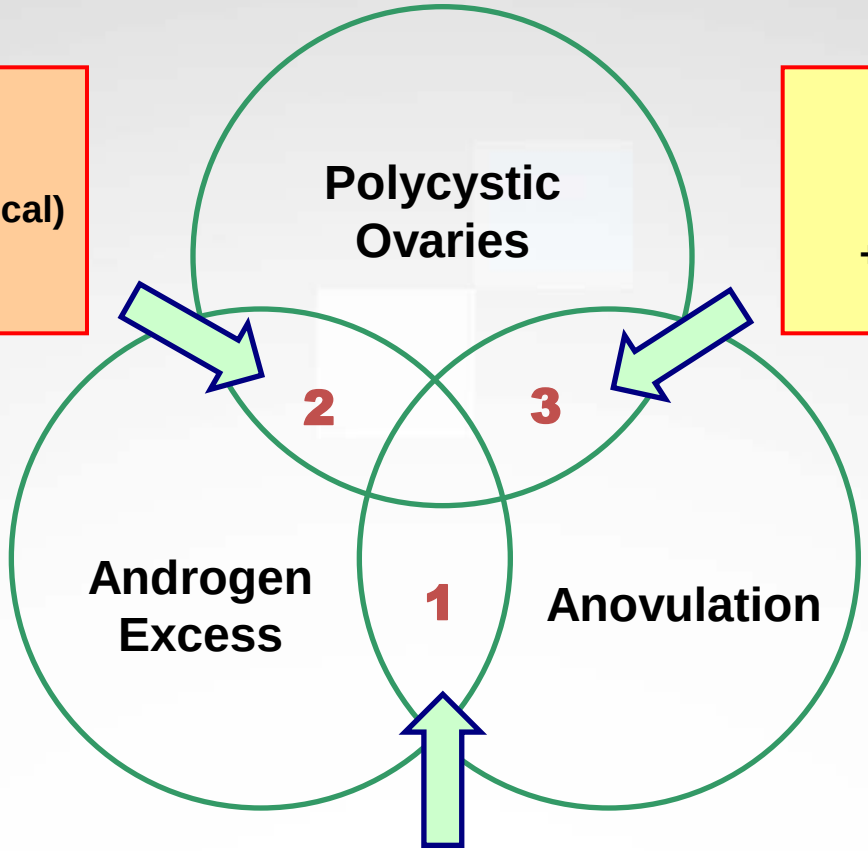
Rotterdam Criteria of PCOS

Area 2
hyperandrogenism
(clinical and/or biochemical)
+ polycystic ovaries
+ regular cycles



Area 3
anovulation
+ polycystic ovaries
+ no evidence of androgen excess

Area 1
NIH criteria 1990

PCOS 환자에서 나이 먹다보면 월경 잘 하는 것 같아……

Once PCOS, Forever PCOS?

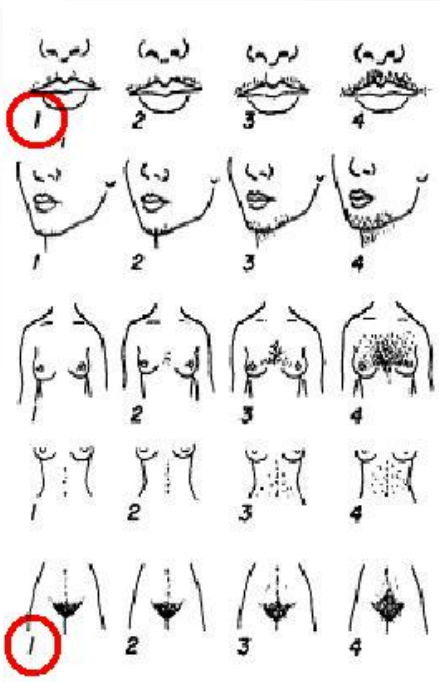
As a PCOS woman grows older	NATIONAL INSTITUTES OF HEALTH Evidence-based Methodology Workshop on Polycystic Ovary Syndrome December 3–5, 2012
Ovulatory Dysfunction	Normal ovulation varies over a woman's lifetime
Androgen Excess	Concentrations differ with age
Polycystic ovarian Morphology	Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence) as ovarian morphology varies with age

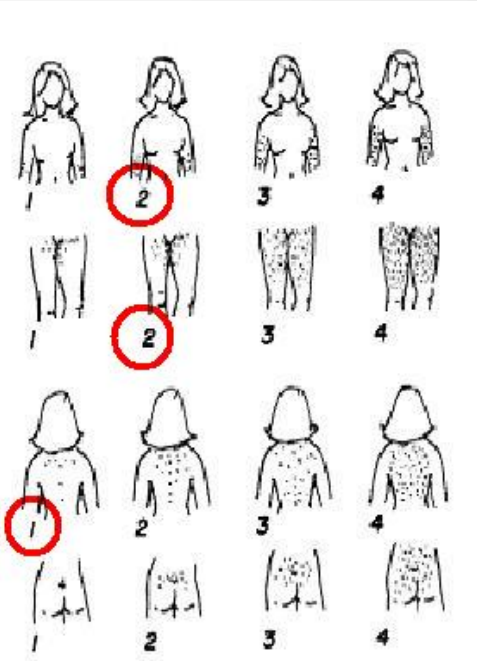
- **The diagnostic features of PCOS may change with age.**

Welt & Carmina. *J Clin Endocrinol Metab.* 2013;98(12):4629-38

- A 32
- P -0-/ single
- LMP 2014-12-05
- 2014-12-24
  - 초경 후 지속되는 Irregular menses 로 방문 (2-3달에 한번 정도)

    => **4-5개월 전부터 규칙적**
  - H-score> 7





- TV-USG> EMT 0.48, AFC R(26), L(21), vol (R 6.03, L 12.0)
- AMH> 16.7▲, MCD#3 LH/FSH/E2> 1.5/ 3.8/ 3 이하
- TSH/PRL> 1.46/ 4.4, Luteal phase P4> 11.39- 5.83
- T/17-OHP/DHEA-S/SHBG> 0.17/ 1.19/ 1106/ 83.5
- 75g OGTT 85/69, HbA1C 5.2

The Change of Androgen Level in PCOS

Androgen in Normal Population

Participants

1423 women recruited from telephone survey
Exclusion (previous hormone therapy, Bilat. Oophorectomy, hysterectomy, T-L, HPRL, PCOS)

Age	18-24	25-34	35-44	45-54	55-64	65-75	P
n	22	97	153	140	74	109	
Mean							
Total T (nM/L)	1.58	1.11	0.92	0.81	0.66	0.71	<0.001
Free T (pM/L)	23.61	17.25	13.67	11.82	10.81	9.76	<0.001
DHEAS (uM/L)	7.49	4.72	4.31	3.42	2.36	1.76	<0.001
ADD (nM/L)	8.46	6.44	5.15	4.17	3.14	3.07	<0.001

Davison et al. *J Clin Endocrinol Metab.* 2005;90(7):3847-53.

Androgen according to the age in PCOS

Participants

84 PCOS women diagnosed btw 1972 and 1986

PCOS = chr. anovulation

or androgen excess, usually hirsutism

or total T > 2 nM or LH/FSH >2

Variable	Age quartile			
	1 (<37 y)	2 (37–42 y)	3 (42–47 y)	4 (>47 y)
No. of women	21	21	21	21
Age (y)	31.5 ± 4.4	39.6 ± 1.47	44.2 ± 1.29	51 ± 3.18
Body mass index (kg/m^2)	31.7 ± 8.75	32.2 ± 8.79	31.1 ± 8.00	30.0 ± 8.68
T level (ng/dL)	68.6 ± 43.3	61.8 ± 33.4	35.6 ± 20.4*	44.7 ± 39.0*
Non–SHBG T level (ng/dL)	12.8 ± 9.9	15.8 ± 11.5	6.26 ± 3.67*	7.93 ± 7.98*
SHBG level (nM)	174 ± 113	144 ± 103	159 ± 94.7	174 ± 68.7
Insulin level (μU/mL)	22.3 ± 12.9	22.1 ± 13.2	17.5 ± 7.33	20.2 ± 20.0
LH level (mIU/mL)	7.27 ± 6.35	5.87 ± 3.39	13.4 ± 16.6*	14.3 ± 13.6*
FSH level (mIU/mL)	4.60 ± 1.99	6.34 ± 2.85	13.7 ± 14.1*	20.19 ± 19.7*

Note: Values are means (±SD). PCOS = polycystic ovary syndrome.

* Results for quartiles 3 and 4 differ significantly ($P<.01$) from those for quartiles 1 and 2 by the Student *t*-test.

Winters et al. *Fertil Steril.* 2000;73(4):724-9.

Androgen according to the age in PCOS

Participants

472 infertile oligoamenorrheic women (1993~1999)
Oligo/amenorrhea (interval vag. Blding > 35 days)
대상 중 일부는 PCOS (NIH criteria)
= FAI > 4.5 and PCO (mean ov. Vol > 10.8 ml)

	Overall group ($n = 472$)	17–29 years ($n = 302$)	30–42 years ($n = 170$)	*P* value*
Clinical				
Amenorrhoea (*n*)†	115 (24%)	72 (24%)	42 (25%)	NS
Cycle duration in oligomenorrhoeic patients (days)	92±67	93±68	89±67	NS
BMI (kg/m^2)	27.0±6.6	27.2±7.0	26.8±6.0	NS
Testosterone (nmol/l)	2.4±1.0	2.5±1.0	2.2±0.9	0.003
AD (nmol/l)	14.3±6.9	15.0±7.3	13.0±6.0	0.002
DHEAS (umol/l)	7.1±3.4	7.5±3.4	6.5±3.2	0.001
FAI	6.9±7.1	7.2±5.9	6.3±8.6	NS
SHBG (nmol/l)	51.3±33.3	49.5±31.9	55.5±35.4	0.06
Transvaginal sonography				
Mean ovarian volume (ml)	9.3±4.6	9.4±4.6	9.1±4.6	NS
Mean follicle number (*n*)	12.5±6.2	12.9±6.0	11.7±6.4	0.05
PCO (*n*)†	99 (21%)	78 (26%)	22 (13%)	0.001

Bili et al. *Eur J Endocrinol.* 2001;145(6):749-55.

The Change of Androgen in PCOS

Participants	**193 women with PCOS (recruited btw 1985-1990) All records were re-evaluated PCOS diagnosed retrospectively based on the Rotterdam criteria.**
Intervention	**20-Year follow-up**

	Age (y)	Total T	DHEAS	Ovarian Volume
Basal	21.9±2.1	75±26	2.7±1.2	10.9±3.9
After 5 y	27.2±2.2	71±25	2.5±1.1	11±4.1
After 10 y	32.3±1	68±22*	2.2±1.3†	10.7±4
After 15 y	37.5±1.4	65±25†	2.1±0.85†	10.3±3.1
After 20 y	42.8±1.5	59±28†	2.00±0.9†	9.1±3.1†

* $P<.05$ compared with basal levels.
† $P<.01$ compared with basal levels.

Carmina et al. *Obstet Gynecol.* 2012;119(2 Pt 1):263-9.

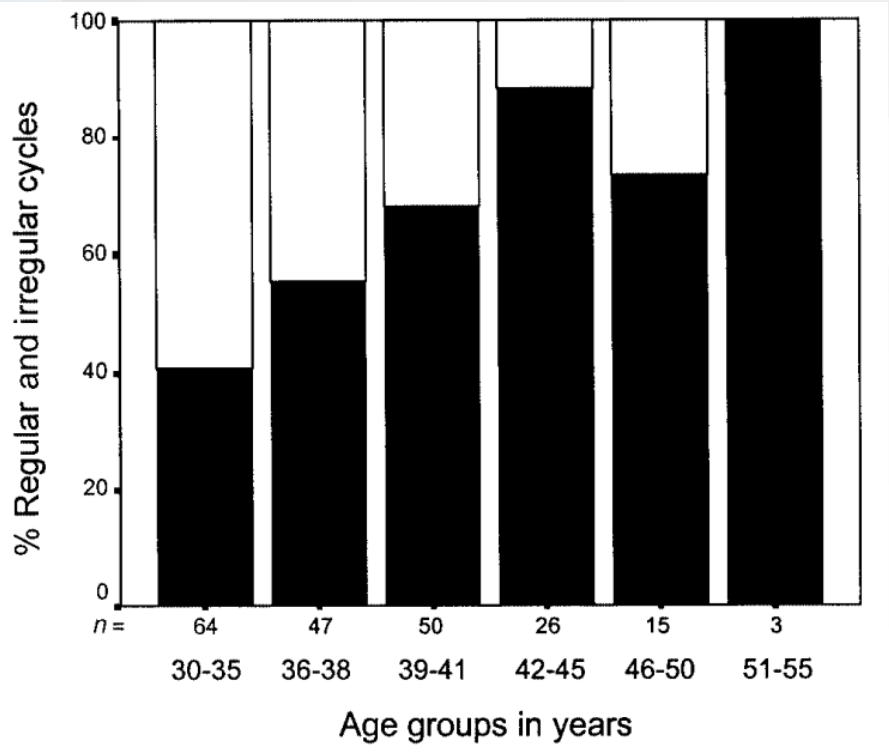
- 정상 여성에서 연령에 따라 남성호르몬은 감소한다.
- PCOS 환자군에서도 연령에 따라 남성호르몬은 차이가 있다.
- PCOS 추적 관찰연구에서는 시간이 지남에 따라 남성호르몬은 감소하였다.

Menstrual Cycles in PCOS

Menstrual Cycles in PCOS

Participants

205 PCOS women with 12-year follow-up
The criteria of PCOS - not documented



■ = regular, □ = irregular

- Change in menstrual cycle pattern = 144/205 (70.2%)
- Shorter cycles = 137/144 (95.1%)

Elting et al. *Hum Reprod.* 2000;15(1):24-8.

Menstrual Cycles in PCOS

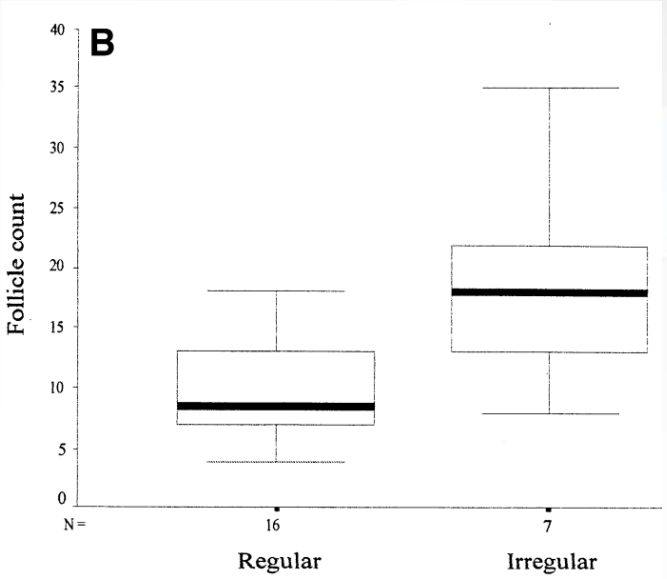
Participants

23 PCOS women
PCOS = Oligo/amenorrhea
+ inc. LH/ normal FSH (MCD#14~ 3 wks before menses)

Intervention

Exogenous FSH ovarian reserve test (EFORT)
rFSH 300 IU

AFC = R+L	Regular (n = 16)	Irregular (n = 7)	*P* value[a]
Day 2, 3, or 4			
Follicle count	8.5 (4.0–18.0)	18.0 (8.0–35.0)	.009
24 h later			
Follicle count	8.5 (3.0–20.0)	20.0 (8.0–35.0)	.01
48 h later			
Follicle count	9.0 (3.0–17.0)	22.0 (9.0–35.0)	.004



Elting et al. *Fertil Steril.* 2003;79(5):1154-60.

AMH & Menstrual Cycles in PCOS

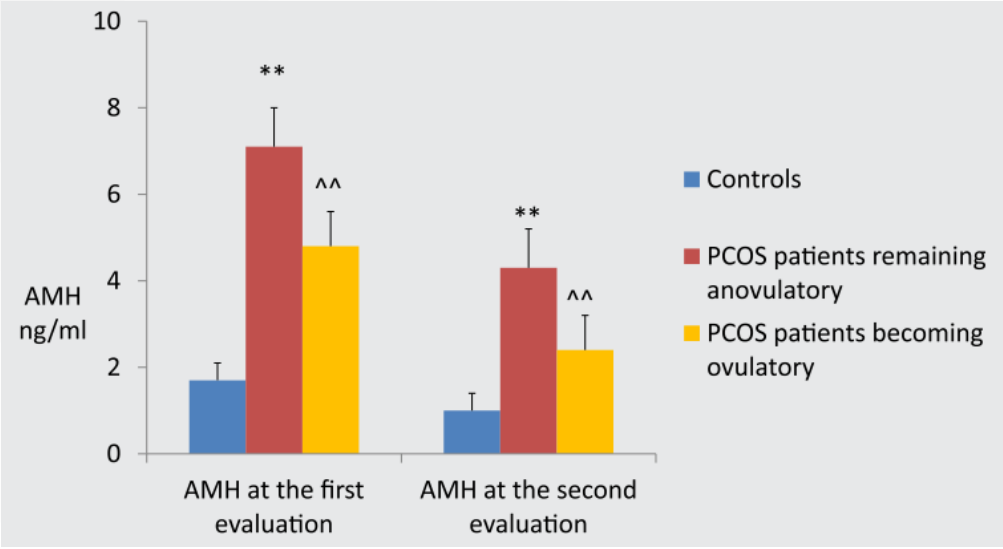
Participants

54 women with PCOS by Rotterdam criteria
20 Age and weight-matched ovulatory control

Intervention

Evaluation initially and again after 5 years

	Age, y	BMI, kg/m^2	LH, mUI/mL	LH/FSH ratio	T, ng/dL	DHEAS, μg/mL	AMH, ng/mL
PCOS	37 ± 1	28 ± 6	10 ± 3.7	1.6 ± 0.7	74 ± 22	2.4 ± 1	6.7 ± 2.1
Control	37 ± 1	27.4 ± 3	6.4 ± 1.4	1.1 ± 0.2	28 ± 11	1.8 ± 1	1.7 ± 0.7
PCOS	42 ± 1	28 ± 6	8.8 ± 4	1.5 ± 0.7	58 ± 19	2.2 ± 1.2	3.9 ± 1.2
Control	42 ± 1	28 ± 4	6.5 ± 1.1	1 ± 0.3	25 ± 16	1.7 ± 1	1 ± 0.7



■ A lower AMH level is associated with the chance of ovulatory function.

■ PCOS women with AMH < 5 ng/mL = a 60% probability to ovulate by age 42

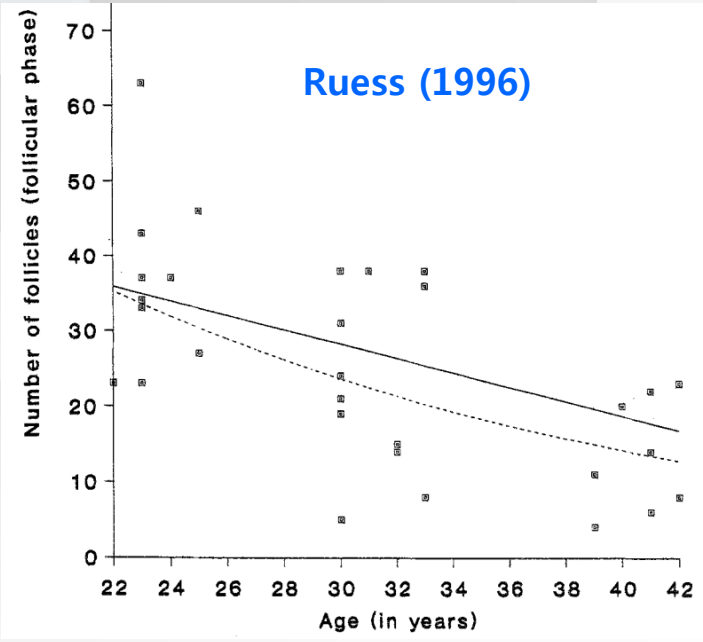
■ All women having values≤ 4 ng/mL had ovulatory function.

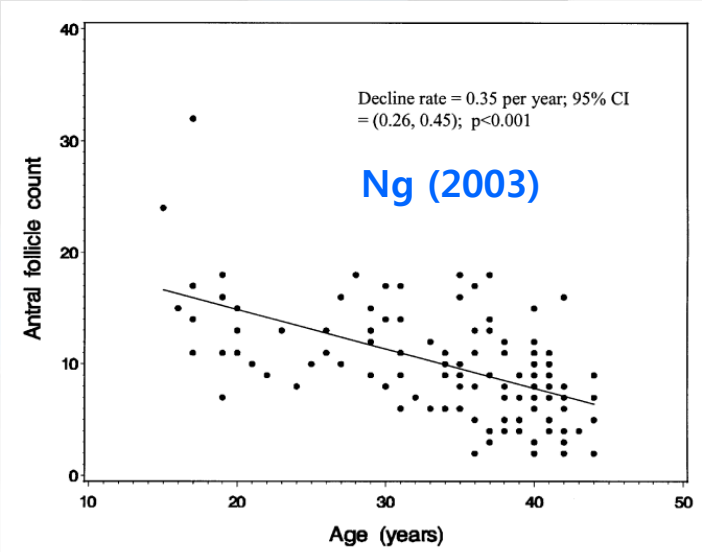
Carmina et al. *Fertil Steril.* 2012;98(4):1043-6

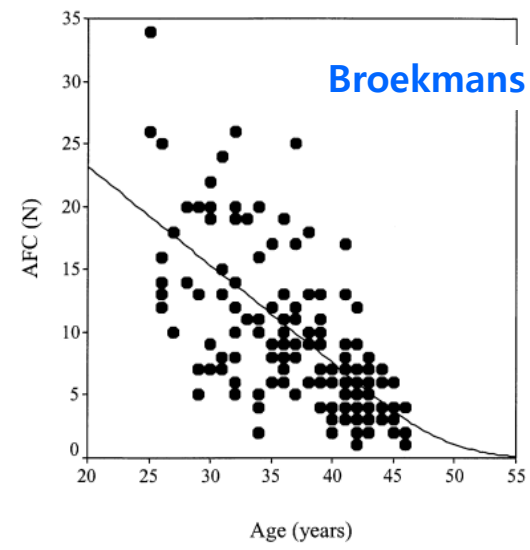
- PCOS 에서 나이를 먹으면서 규칙적 월경을 경험할 수 있다.
- PCOS 에서 규칙적 월경은 AMH 농도와 관련이 있을 수 있다.

AFC and Ovarian Volume in PCOS

AFC according to the Age in General Population



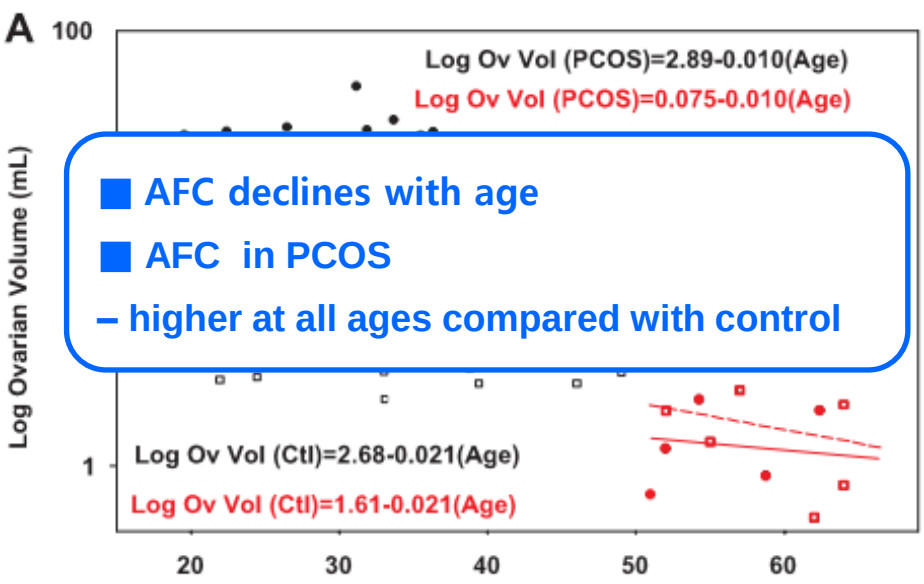


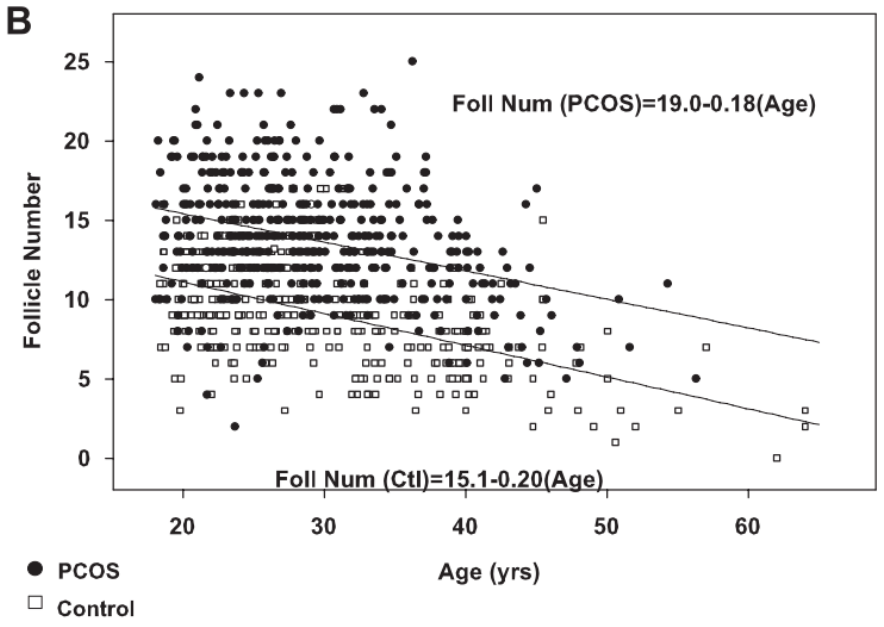


Ruess et al. *Am J Obstet Gynecol.* 1996;174(2):624-7.
Ng et al. *Hum Reprod.* 2003;18(10):2169-74.
Broekmans et al. *Menopause*. 2004;11(6 Pt 1):607-14.

AFC according to the Age in PCOS

Participants	11 women with PCOS = oligomenorrhea + hyperandrogenism (or -genemia) (USG criteria - not included) 15 age-matched ovulatory control
Intervention	Evaluation initially and again after 7-15 years





Alsamari et al. *J Clin Endocrinol Metab.* 2009;94(12):4961-70.

- 일반인뿐만 아니라 PCOS 에서도

  나이를 먹으면서 antral follicle count 및 난소 용적은 감소한다.

- AFC는 전 연령에서 일반인보다 PCOS에서 많이 관찰된다.

A Model to Predict PCOS at all Ages

Participants	11 women with PCOS = oligomenorrhea + hyperandrogenism (or -genemia) (USG criteria - not included) 15 age-matched ovulatory control
Intervention	Evaluation initially and again after 7-15 years

■ log (odds of PCOS) = -10.1302 + 0.0978 x age + 0.2698 x follicle number + 0.6967 x log volume + 0.0632 x testosterone (ng/dl)

■ A log (odds of PCOS) score of 0.51 or higher
- a specificity of 83% and a sensitivity of 83% for predicting PCOS.

Alsamari et al. *J Clin Endocrinol Metab.* 2009;94(12):4961-70.

- 폐경이 되면 특징적 소견들이 사라지기 때문에 PCOS를 진단하는 것은 불가능하다.
- One is able to make the diagnosis of PCOS only during the reproductive years.

Metabolic Features in PCOS

Does Diabetes Increase in PCOS F/U Study?

Participants

277 women with PCOS, evaluated from 1978 to 1999, were contacted

NIH Criteria

255 women with PCOS visited again in 2009 and were included in the comparison of type 2 DM with general population

Variables	DM	Hazard ratio (95% CI)	*P**
Age at follow-up, 5-year increase		0.95 (0.89–1.01)	0.059
Baseline BMI, one-point increase		1.10 (1.06–1.14)	<0.001
Baseline fasting glucose, 10 mg/dL increase		1.52 (1.01–2.29)	0.043
Logarithm of SHBG at follow-up, 1 nmol/L increase†		0.12 (0.06–0.26)	<0.001

	n/*N* (person-years of follow-up)	Incidence rate (95% CI) × 100 person-years
Overall sample	42/249 (4,018)	1.05 (0.75–1.41)
BMI class (kg/m^2)		
<25	3/79 (1,216)	0.25 (0.05–0.72)
25–29.99	8/78 (1,269)	0.63 (0.27–1.24)
≥30	31/92 (1,533)	2.02 (1.38–2.86)

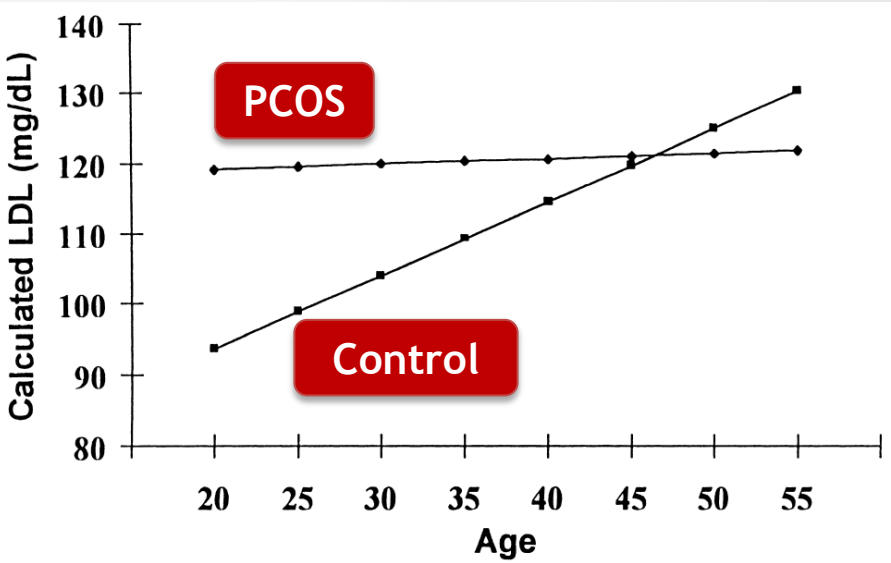
Gambineri et al. *Diabetes.* 2012;61(9):2369-74.

The Change of Cholesterol in PCOS

Participants

244 PCOS women (NIH Criteria) vs control (n=244)
chr anovulation + (1) clinical evidence of androgen excess or (2) total T> 2 nmol/L or LH/FSH > 2

Variable	Cases (n = 244)	Controls (n = 244)
Age	35.3 ± 7.4	36.7 ± 7.7
Body mass index (kg/m^2)	29.9 ± 7.95	26.6 ± 6.77[a]
Waist-hip ratio	0.83 ± 0.13	0.76 ± 0.07[a]
Total cholesterol (mg/dL)	195.8 ± 32.95	185.7 ± 36.34[a]
HDL-T (mg/dL)	51.2 ± 14.74	56.1 ± 14.43[a]
HDL-2 (mg/dL)	8.4 ± 6.5	11.4 ± 7.78[a]
LDL-C (mg/dL)	119.9 ± 31.8	112 ± 32.6[a]
Insulin (μU/L)	23.3 ± 17.8	13.6 ± 8.7[a]
Triglycerides (mg/dL)	123.6 ± 88.7	87.3 ± 63.1[a]
Average systolic blood pressure (mm Hg)	113.5 ± 14.7	110.3 ± 13.1[a]
Diastolic blood pressure (mm Hg)	72.7 ± 10.5	70.8 ± 8.3[b]



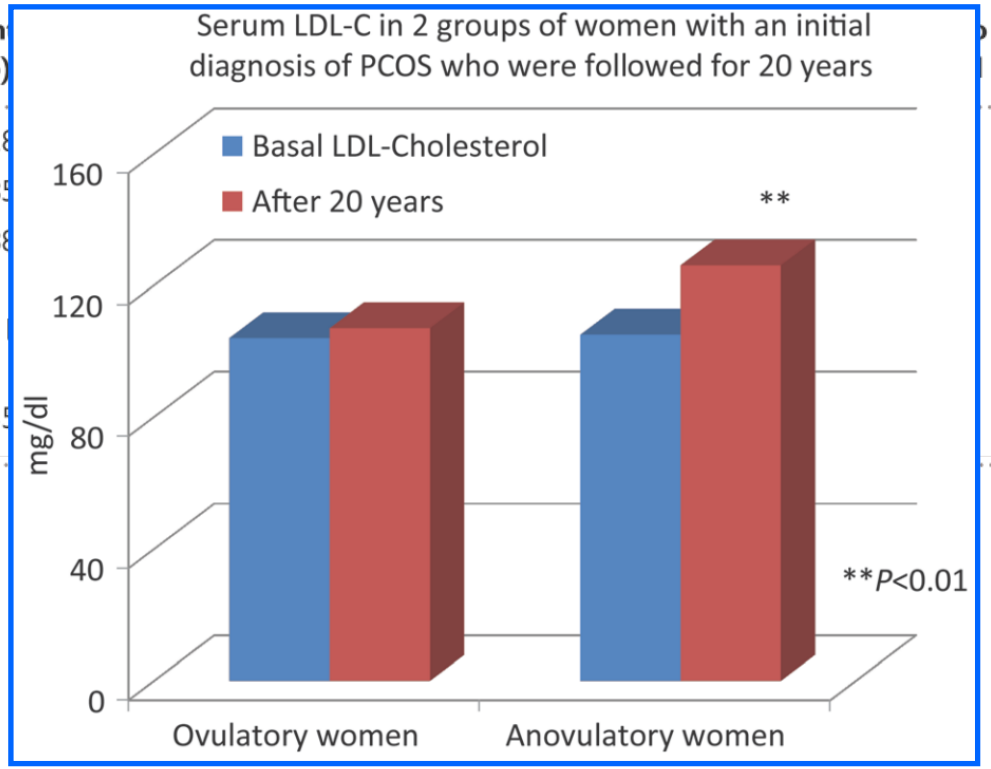
Talbott et al. *J Clin Epidemiol.* 1998;51(5):415-22.

Metabolic Risk & Increased Ovulation

Participants

97 PCOS women (recruited btw 1985-1990)
Retrospective PCOS Dx based on the Rotterdam criteria
30 ovulatory PCOS vs 67 anovulatory PCOS

	Con (Co)		versus for BMI	*P* value, Co versus A	*P* value, Co versus A adjusted for BMI
BMI	23.8			0.009	—
Waist (cm)	85			0.004	0.06
Glucose (mg/dl)	88			0.038	0.075
Insulin (μU/ml)				0.006	0.009
QUICKI	0.335			0.004	0.009
Total C (mg/dl)				0.006	0.008
HDL-C (mg/dl)				0.004	0.004
TG (mg/dl)				0.097	0.167
LDL-C (mg/dl)				0.004	0.009
Non-HDL-C (mg/dl)				0.004	0.008



P should be less than 0.017

Carmina et al. *Hum Reprod.* 2013;28(8):2245-52.

The Change of Metabolic Features in PCOS

Participants

11 women with PCOS
= oligomenorrhea + hyperandrogenism (or -genemia)
15 age-matched ovulatory control

Intervention

Evaluation initially and again after 7-15 years

	PCOS		Control		*P* values	
	Younger	Older	Younger	Older	PCOS/CTL	Dx/time
Age (yr)	36.5 ± 3.3	46.3 ± 4.2[a]	35.3 ± 5.3	46.0 ± 4.5[a]	0.5	0.1
BMI (kg/m^2)	32.3 ± 10.6	32.1 ± 9.3	23.7 ± 4.6	26.5 ± 5.7	0.01	0.2
Cholesterol (mg/dl)	199.7 ± 37.5	226.5 ± 33.5[a]	158.2 ± 26.3	190.7 ± 26.7[a]	0.07	0.8
Triglyceride (mg/dl)	161.5 ± 93.7	173.5 ± 91.0	72.8 ± 30.5	74.9 ± 27.7	0.04	0.5
HDL (mg/dl)	37.6 ± 14.8	50.0 ± 12.3	50.5 ± 7.8	60.3 ± 16.7	0.5	0.4
LDL (mg/dl)	128.4 ± 31.7	140.0 ± 35.7	93.0 ± 26.8	115.4 ± 27.7	0.1	0.7
Fasting glucose (mg/dl)	92.2 ± 6.4	100.0 ± 21.3	92.7 ± 4.6	86.9 ± 8.3	0.8	0.1
Fasting insulin (μIU/ml)	7.2 ± 4.3	11.3 ± 4.2	4.2 ± 1.4	6.0 ± 3.1	0.3	0.1
HOMA	1.66 ± 0.99	2.50 ± 0.95	0.97 ± 0.34	1.30 ± 0.69	0.3	0.1

[a] Differences between older and younger women within the PCOS and control groups.

- Total cholesterol ▲ & TG▲
- BMI, FBS, Insulin, HOMA: no significant change

Alsamari et al. *J Clin Endocrinol Metab.* 2009;94(12):4961-70.

The Change of Metabolic Features in PCOS

Participants	193 women with PCOS (recruited btw 1985-1990) All records were re-evaluated PCOS diagnosed retrospectively based on the Rotterdam criteria.
Intervention	20-Year follow-up

	Age (y)	BMI (kg/m²)	Waist Circumference (cm)	Insulin	QUICKI
Basal	21.9±2.1	26.6±6.7	88.9±14.5	14.9±6.5	0.327±0.02
After 5 y	27.2±2.2	27.3±7	89.4±12	13.8±7	0.329±0.2
After 10 y	32.3±1	27.5±5.7	90.8±11.5	15.2±8	0.328±0.02
After 15 y	37.5±1.4	26.8±4.5	91.7±11.8*	14.5±6.8	0.332±0.02
After 20 y	42.8±1.5	26.9±5.1	94.7±12.5†	13.5±4.5	0.329±0.02

* $P<.05$ compared with basal levels.
† $P<.01$ compared with basal levels.

- WC▲
- BMI, Insulin, QUICKI: no significant change

Carmina et al. *Obstet Gynecol.* 2012;119(2 Pt 1):263-9.

Cardiovascular Morbidity in PCOS

Participants

1028 women diagnosed with PCOS before 1979 in UK Histopathology records or op record (wedge resection or ovarian biopsy) (76%) or clinical finding

Outcome	Model	OR	95% CI	*P* value
Breast cancer	PCOS	1.5	0.7–2.9	0.3
	PCOS, BMI	1.3	0.6–2.8	0.6
Endometrial cancer	PCOS	5.3	1.5–18.6	0.009
	PCOS, BMI	6.1	1.0–36.9	0.05
Coronary heart disease	PCOS	1.5	0.7–2.9	0.3
	PCOS, BMI	1.2	0.5–2.6	0.7
Diabetes	PCOS	2.8	1.5–5.5	0.002
	PCOS, BMI	2.2	0.9–5.2	0.08
Hypertension	PCOS	1.4	1.0–2.0	0.04
	PCOS, BMI	1.4	0.9–2.0	0.1
High cholesterol	PCOS	2.9	1.6–5.2	< 0.001
	PCOS, BMI	3.2	1.7–6.0	< 0.001

Wild et al. *Clin Endocrinol.* 2000;52(5):595-600.

- PCOS 와 정상 대조군을 젊은 나이부터 폐경에 이르는 동안 추적 관찰한 연구는 거의 없다.
- 심혈관계 위험인자에 더 오래 노출되는 것에도 불구하고, PCOS 환자에서 CVD 증가의 증거는 명확하지 않은 상태이다.

Speroff

Although direct evidence for an increased incidence of cardiovascular disease in women with PCOS is lacking, the prevalence of known risk factors is substantially increased.[504]

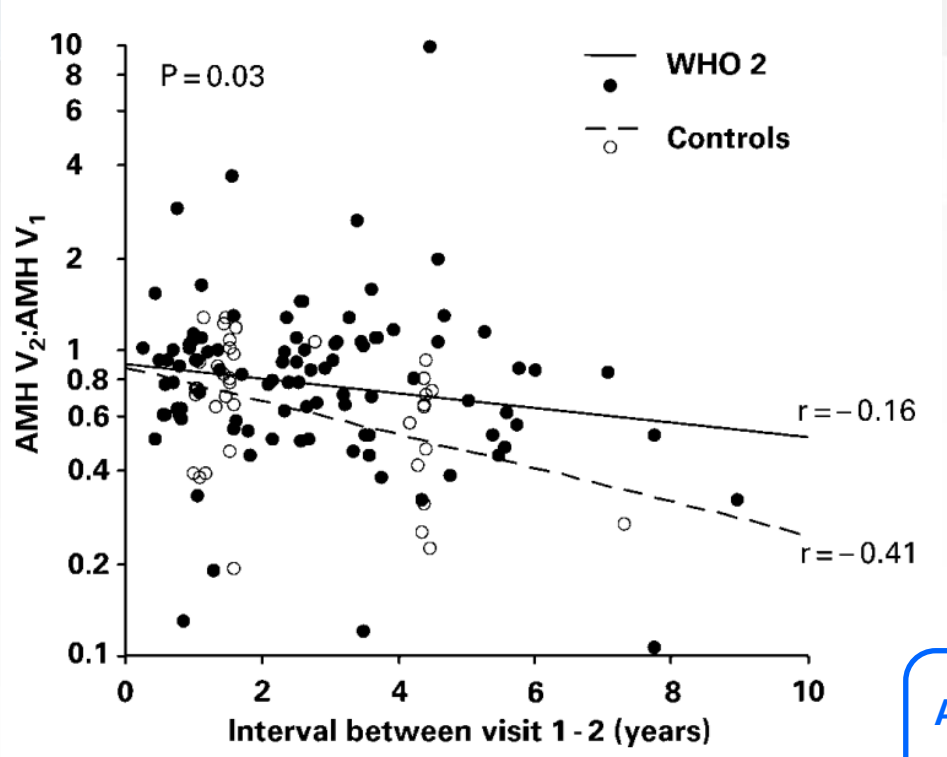
Ecological Aspects in PCOS

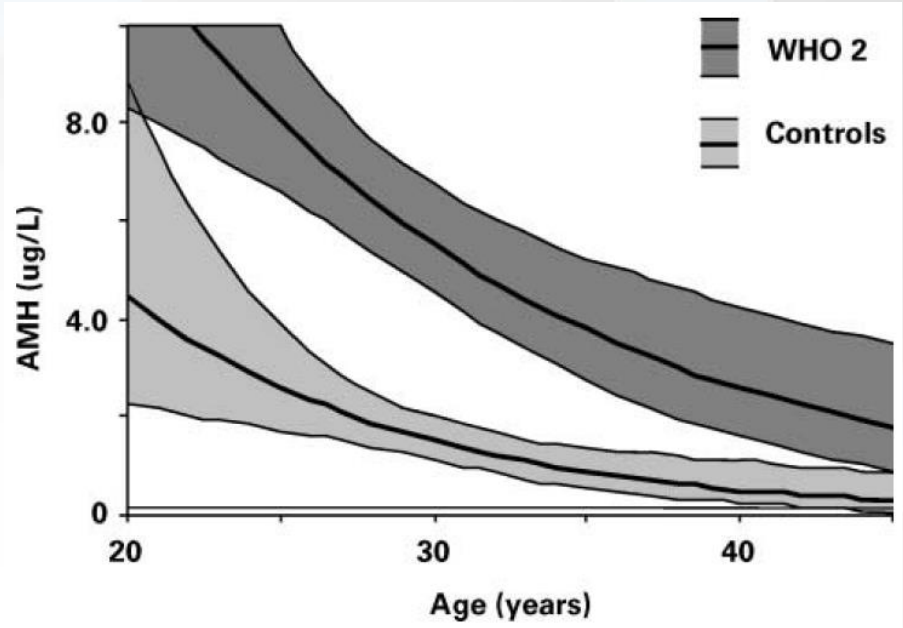
- Selective Advantages in Different Environment
- Thrifty gene hypothesis
  - Metabolic traits
    - advantageous in times of starvation
    - Disadvantageous in the modern world where food is plentiful
    - Results in type 2 DM
- PCOS
  - Longer reproductive lifespan
  - Greater number of follicles and attenuated fall of volume

AMH in WHO type 2 Anovulation Group

Participants

98 women with infertility, oligo/amenorrhea
+ normal FSH (including PCOS)
(WHO type 2 normogonadotropic anovulation)



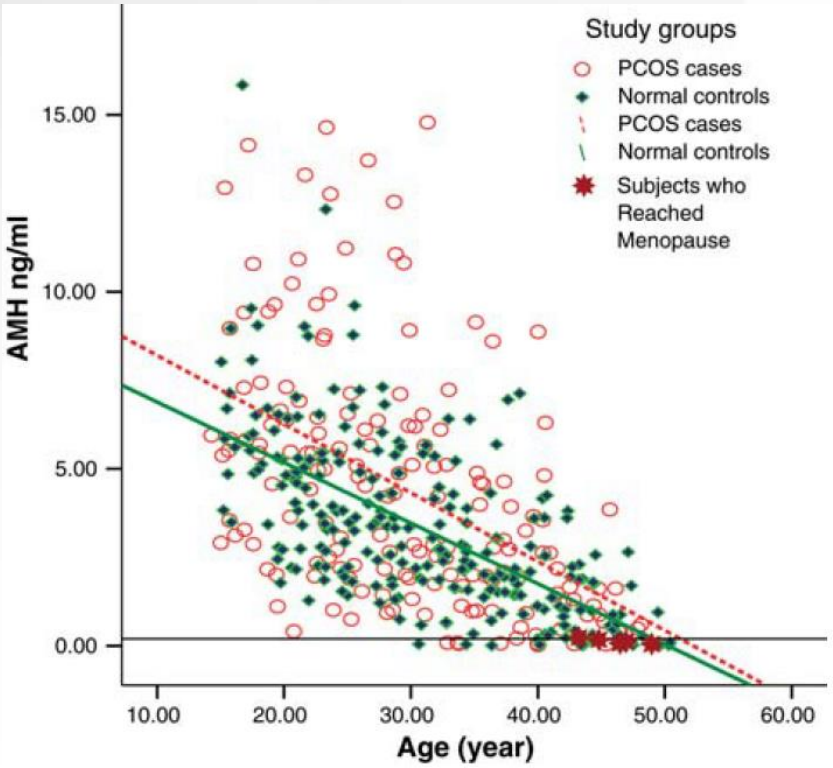


AMH- Less pronounced longitudinal decrease in WHO type 2 anovulation patients

Mulders et al. *Hum Reprod.* 2004;19(9):2036-42.

AMH & Expected MP age in PCOS

Participants	85 PCOS by NIH criteria vs 89 age & BMI-matched controls
Intervention	AMH measurement at 3-year interval (x3)



- **AMH difference**
  - diminished in subsequent assessment
- **Estimated age at MP**
  - 51 (PCOS) vs 49 (Controls)

Tehrani et al. *Hum Reprod.* 2010;25(7):1775-81.

Age at Menopause in PCOS

Participants

1028 women diagnosed with PCOS before 1979 in UK
Histopathology records or op record (wedge resection or ovarian biopsy) (76%) or clinical finding

- Age at MP: 47.5 (PCOS) vs 47.6 (Control), P=0.90

Wild et al. *Clin Endocrinol (Oxf).* 2000;52(5):595-600.

Participants

30 women diagnosed with PCOS before 1965
Hx of wedge resection or unilat. oophorectomy
21-Yr F/U study

- Age at MP: 50.1 (PCOS) vs 51.6 (Control), P=0.41

Schmidt et al. *J Clin Endocrinol Metab.* 2011;96(7):2178-85.

- PCOS에서는 AMH 감소가 대조군에 비해 덜 두드러지게 나타날 수 있다.
- PCOS 에서는 reproductive lifespan 이 길 수 있을 것으로 보이나 모든 연구에서 증명된 것은 아니며, 후속 연구가 필요하다.

Conclusions

- The phenotypes of PCOS changes across the lifespan.
- Age-based criteria to diagnose PCOS is needed.
- Follow-up of PCOS women up to menopause will provide the data for the true CVD risk.


Thank You
for Your Attention!
서울대학교병원