Predicting menopausal age with Anti-Müllerian hormone?

Prof.Dr.Sezai ŞAHMAY

İ.Ü.Cerrahpaşa Tıp Fakültesi
Kadın hastalıkları ve Doğum ABD
Üreme Endokrinolojisi ve İnfertilite Bilim Dalı Başkanı

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Stages of Reproductive Aging Workshop - STRAW

Menarche — FMP (0)

Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

Harlow SD et al.:J Clin Endocrinol Metab 97: 1159–1168, 2012

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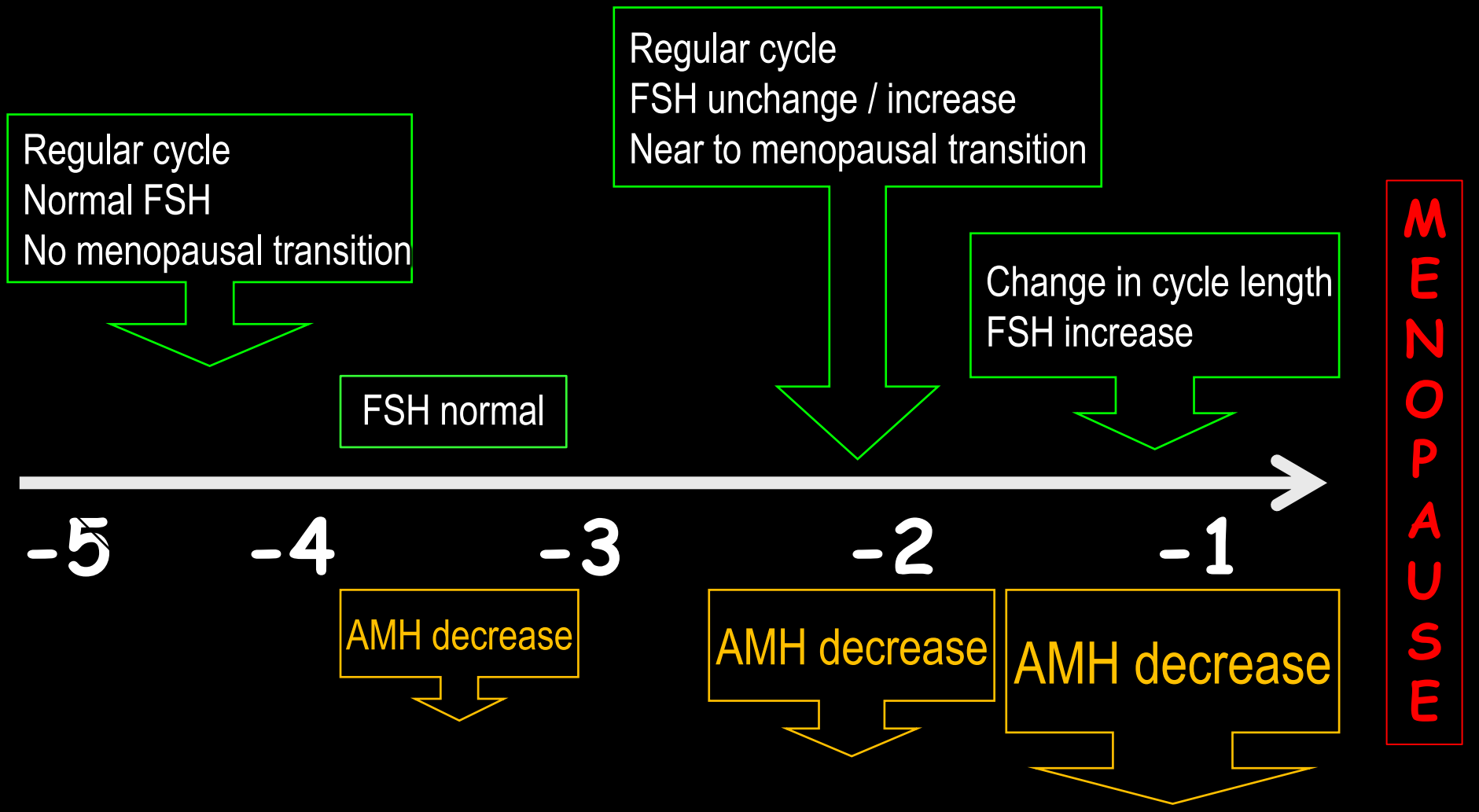
Stages of Reproductive Aging Workshop - STRAW



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Ovarian primordial and nongrowing follicle counts, total ovarian antral follicle counts, and biomarkers of ovarian reserve for STRAWstages

PDF

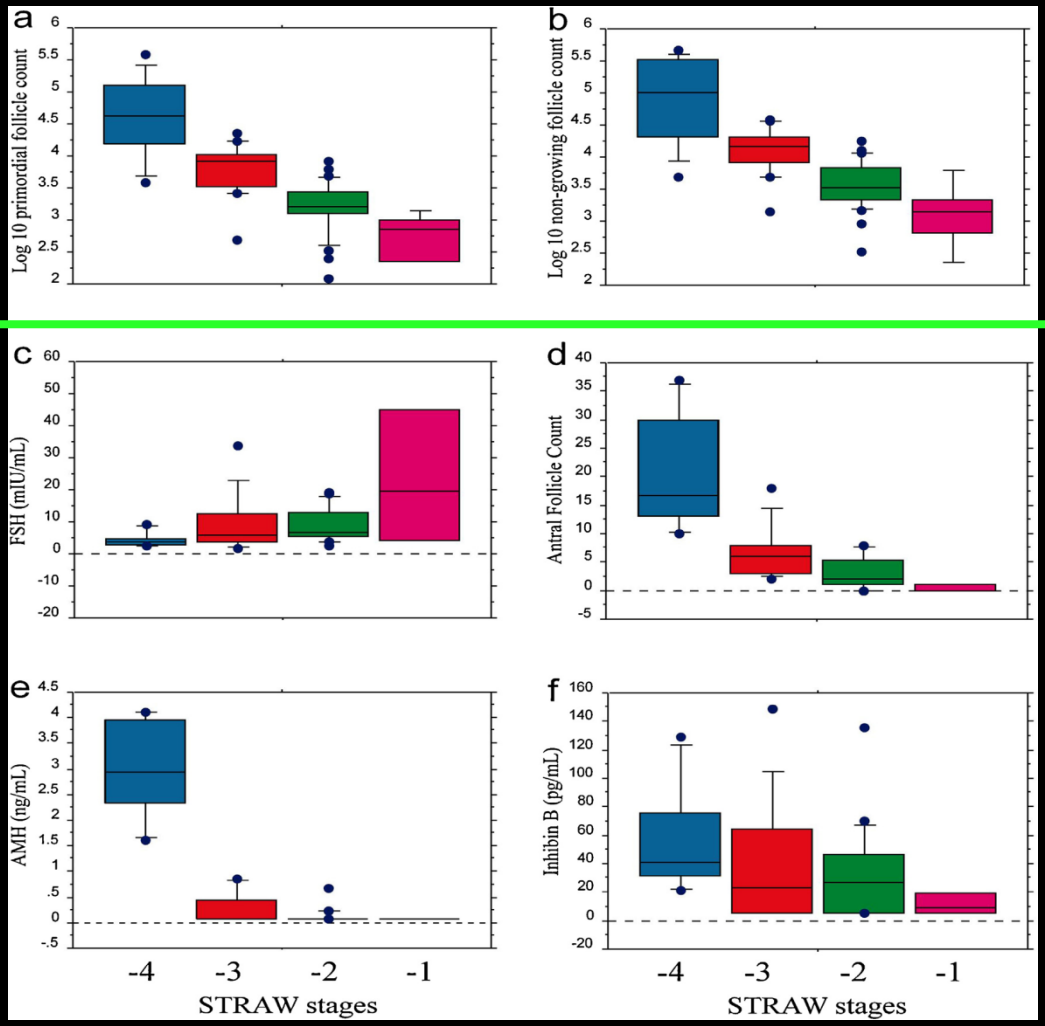
NGF

FSH

AFC

AMH

INH-B



Hale GE, et al.,:J. Steroid Biochem. Mol. Biol. (2013)

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When AMH levels fall below detectable levels, women at the menopausal transition will progress to menopause within 3 years.

TABLE 2. *Changes in serum AMH levels during the years around FMP in group A*

Menopause group

	Years to FMP								
	−5	−4	−3	−2	−1	FMP	+1	+2	+3
Number of samples	5	8	15	21	27	26	21	11	5
Proportion of STRAW stage −1, %	0	0	35.7	60.0	92.3	–	–	–	–
Proportion of AMH undetectable, %	20.0	62.5	100	100	100	100	100	100	100
AMH, mean ± SD, ng/mL[a]	0.18 ± 0.08[b]	0.09 ± 0.02	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08

AMH, antimüllerian hormone; FMP, final menstrual period; STRAW, Stages of Reproductive Aging Workshop.
[a]Values show population-level data.
[b]$P < 0.01$ versus the AMH levels in FMP (Tukey's multiple comparison test).

n.29

TABLE 3. *Changes in serum AMH levels during the years around the menopausal transition in group B*

Regüler-İrregüler cycles

	Years to the menopausal transition							
	−5	−4	−3	−2	−1	0[a]	+1	+2
Number of sample	7	10	13	14	10	15	6	3
Proportion of AMH undetectable, %	28.6	30.0	61.5	71.4	90.0	93.3	100	100
AMH, mean ± SD, ng/mL[b]	0.38 ± 0.31[c]	0.27 ± 0.18[c]	0.14 ± 0.10	0.13 ± 0.10	0.10 ± 0.06	0.08 ± 0.01	<0.08	<0.08

AMH, antimüllerian hormone.
[a]The first year that menstrual cycle became irregular.
[b]Values show population-level data.
[c]$P < 0.01$ versus the AMH levels in the final menstrual period (Tukey's multiple comparison test).

n.15

Kaori I et al.:Menopause, Vol. 20, No. 2, 2013

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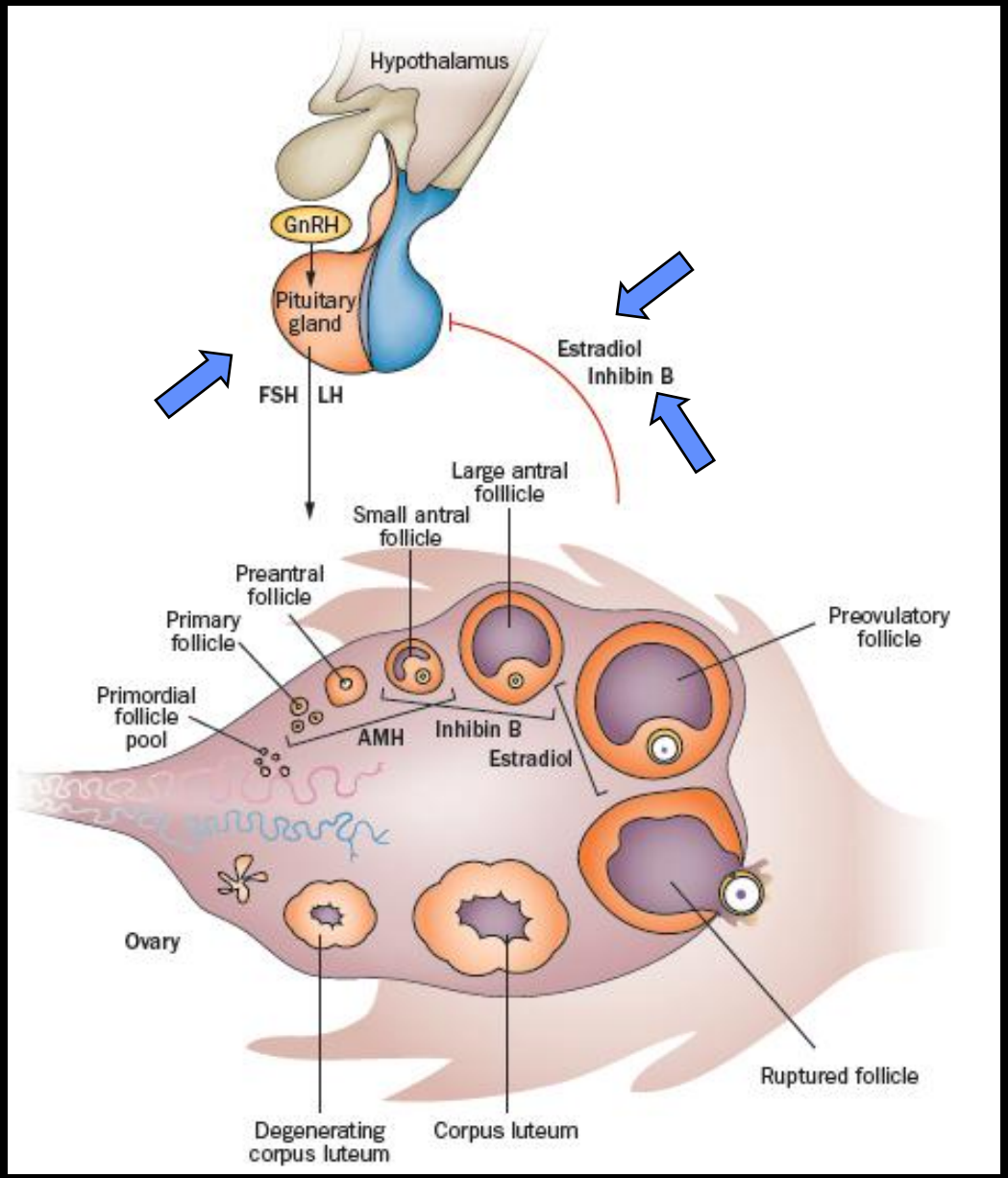
Relationship endocrine and USG findings with age.

Parametre	Relation with Age
FSH	+
LH	-
İnhibin-B	+
Östradiol	+
Progesteron	-
Anti-Müllerien hormon	+++
Over volümü	+
Antral Folikül sayısı	++



- Secretion from primary and small antral folicles.
- Secretion from granulosa cells.
- Minimal interaction with FSH.
- Only marker for ovarian folicular function.

Visser, J. A. et al. Nat. Rev. Endocrinol 10:331, 2012

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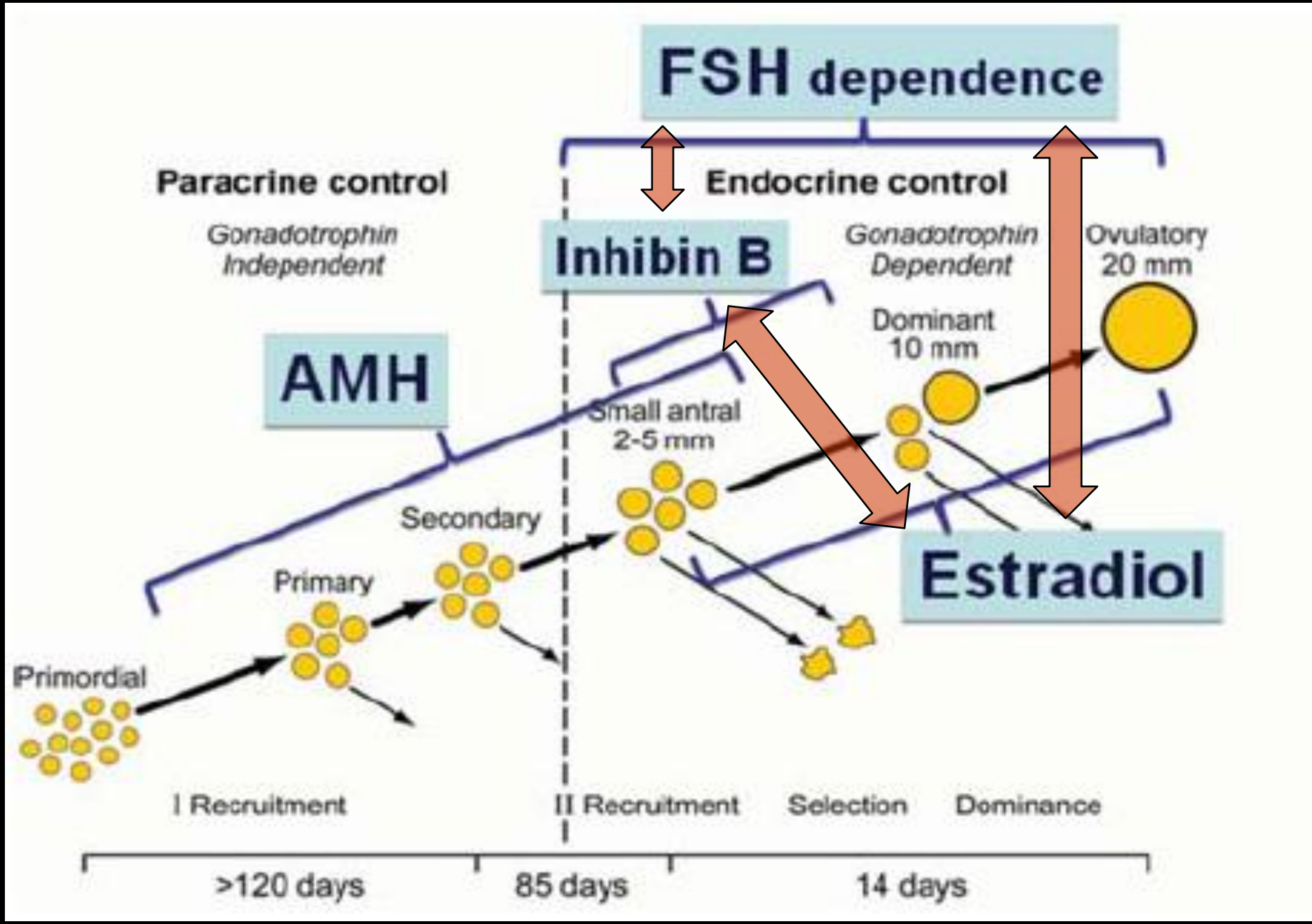

La Marca A. Et al.:Human Reproduction, Vol.24, No.9 pp. 2264-2275, 2009

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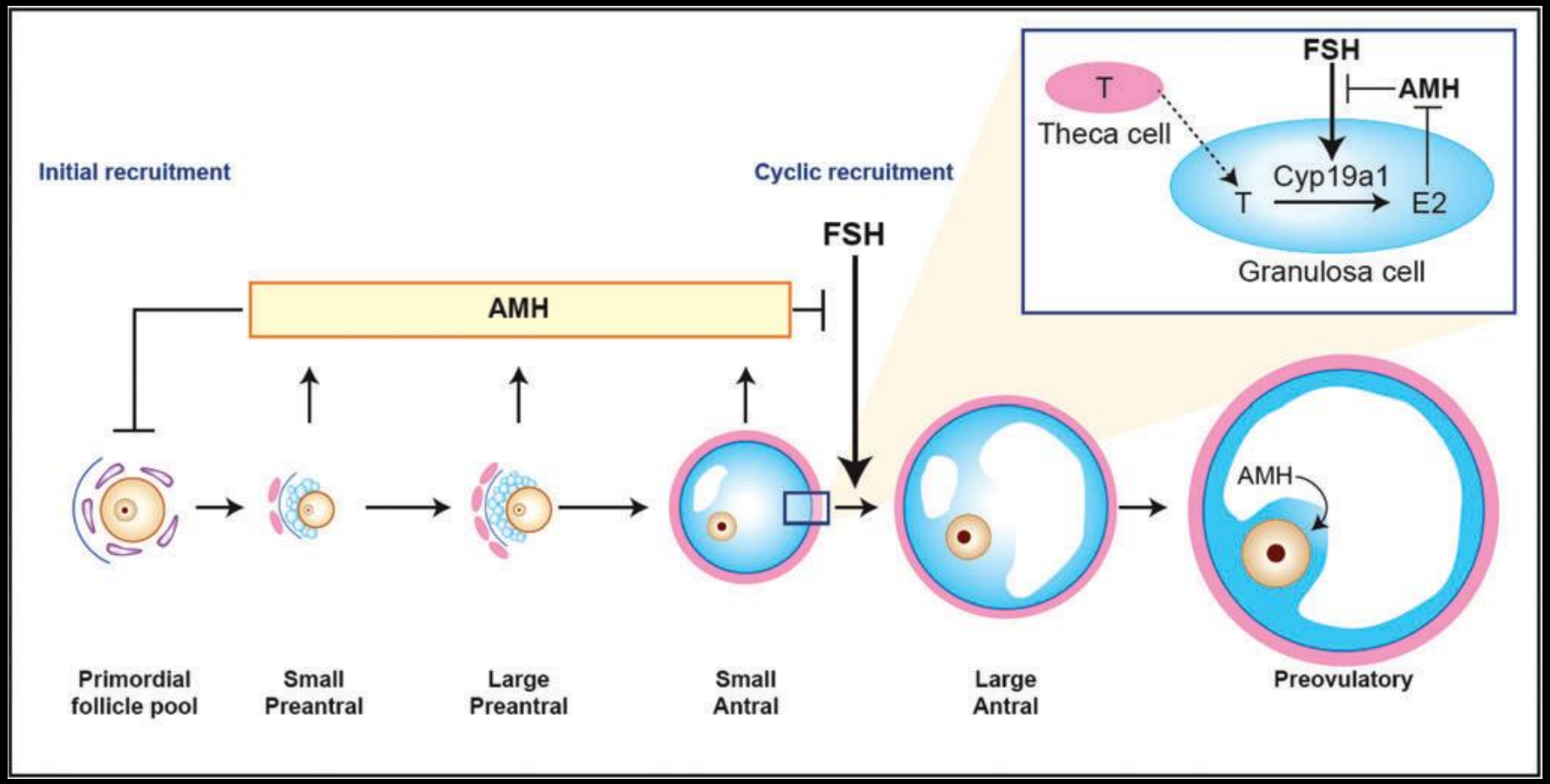
Schematic model of AMH actions in the ovary



Dewailly D et al.: Human Reproduction Update, 20: 370–385, 2014

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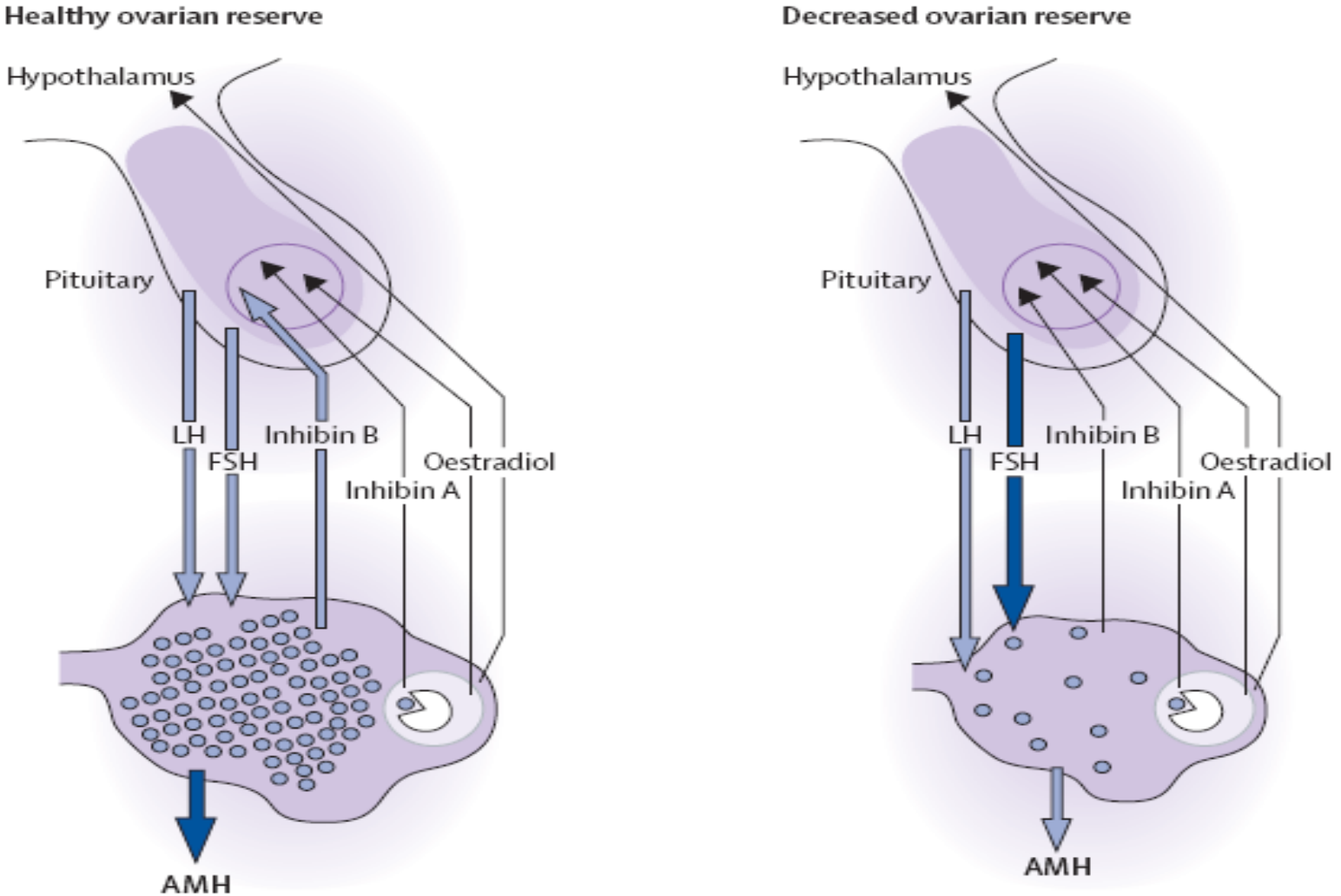
Decreased follicles in menopausal transition



De Vos M et al.:Lancet 2010; 376: 911–21

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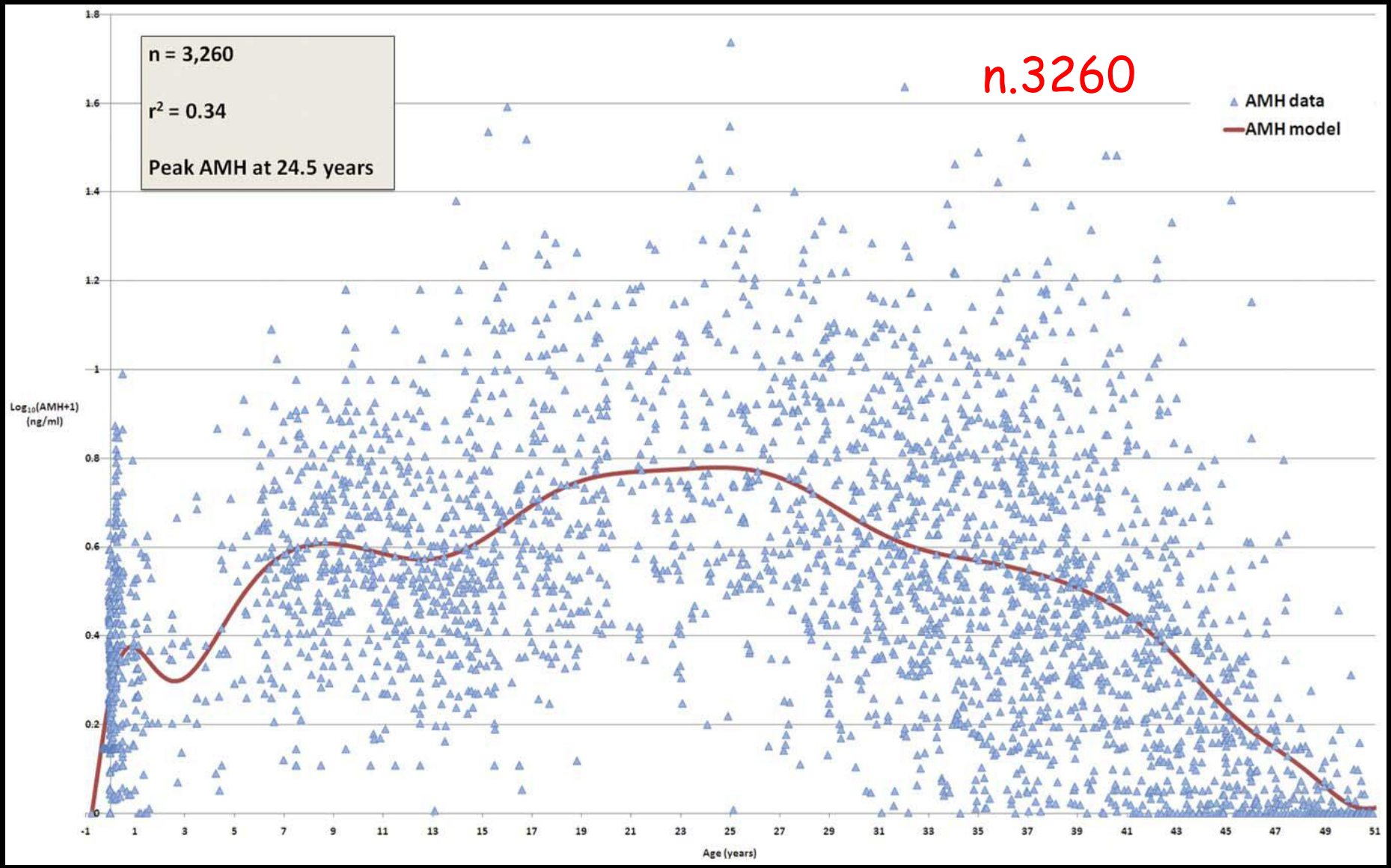
AMH from intrauterine life to menopause



Kelsey TW et al.: doi:10.1371/journal.pone.0022024, 2011

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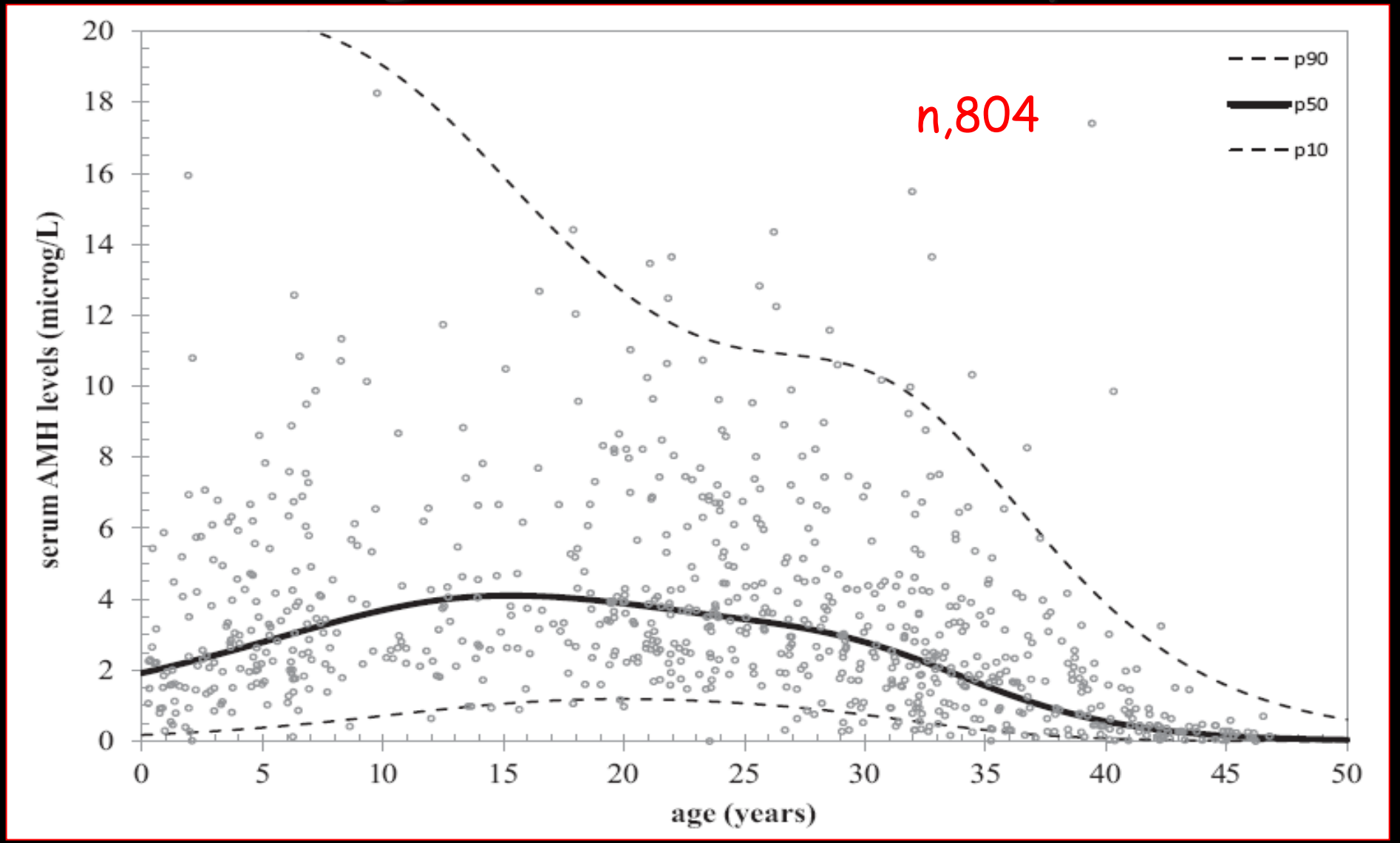
AMH nomograms: %10-%50-%90 percentile



Lie Fong S et al.: J Clin Endocrinol Metab 97: 4650–4655, 2012

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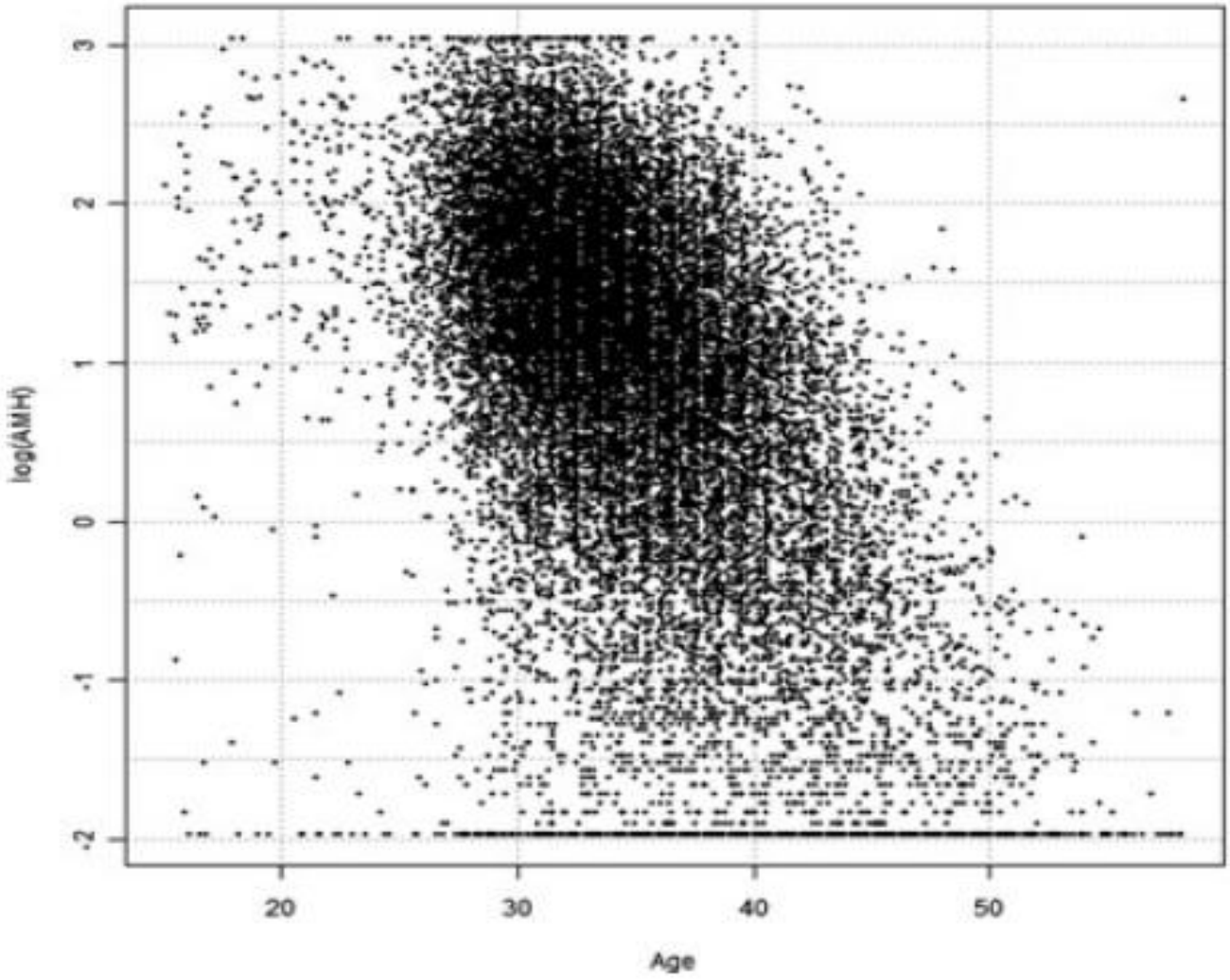
AMH values vs age n.21226



Age	No	Age	No	Age	No
15	4	30	1699	45	215
16	8	31	1868	46	136
17	6	32	1912	47	97
18	17	33	1895	48	121
19	7	34	1692	49	79
20	7	35	1505	50	66
21	25	36	1401	51	30
22	21	37	1103	52	31
23	23	38	1050	53	25
24	48	39	834	54	28
25	111	40	614	55	3
26	223	41	476	56	19
27	508	42	449	57	2
28	922	43	348	58	11
29	1305	44	299		

n.21226

Lee JY et al.: Acta Obstetricia et Gynecologica Scandinavica 91:970, 2012

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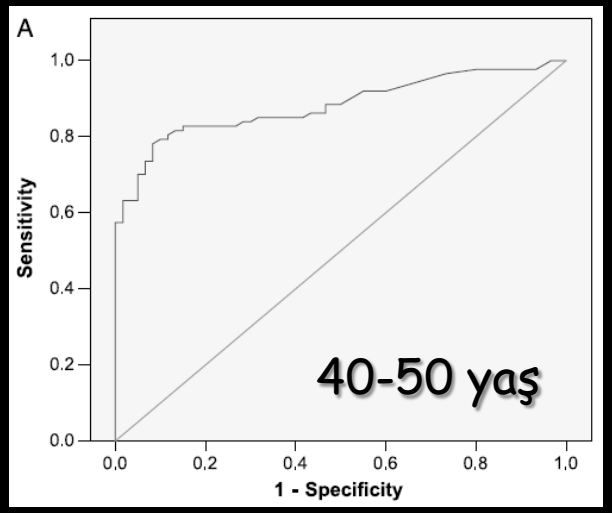
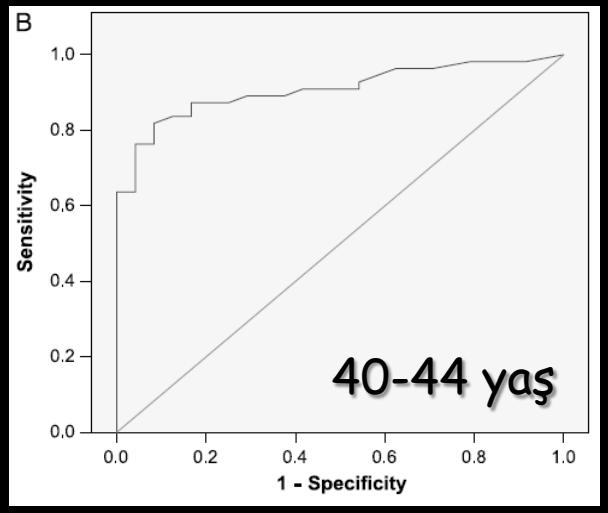
Only one AMH test can predict menapausal age.
(147 women 3 AMH measurement in 3 year interval)





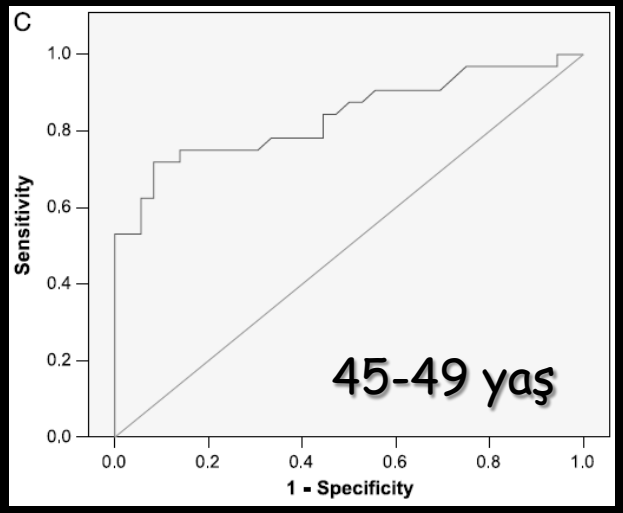


TABLE 2. *Sensitivity, specificity, and area under the curve for prediction of not entering menopause by cutoff points of AMH in different age groups*

	No. participants	AUC (95% CI)	Cutoff point, ng/mL	Sensitivity	Specificity
All participants age 40-49 y	147	0.88 (0.83-0.94)	0.39	0.82	0.87
Subgroup age 40-44 y	79	0.87 (0.78-0.96)	0.49	0.82	0.92
Subgroup age 45-49 y	68	0.81 (0.70-0.92)	0.365	0.75	0.86

AMH, antimüllerian hormone; AUC, area under the receiver operating characteristics curve.

Every 10 women in their late reproductive age (40-50 y), only one will reach menopause status within 6 years if she has an AMH level greater than 0.39 ng/mL.

Tehrani FR et al.:Menopause 16:797, 2009

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Modeling Age at Menopause Using Serum concentration of Anti-Mullerian Hormone 20-50 ages 1015 women (10 years)

AMH, ng/dL	Age, y							
	20	22	24	26	28	30	32	34
0.1	33 (27–36)	34 (28–38)	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)
0.3	34 (28–38)	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)
0.5	35 (29–39)	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)
0.7	36 (30–40)	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)
0.9	37 (31–41)	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)
1.1	39 (32–43)	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)
1.3	40 (33–44)	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)
1.5	41 (34–46)	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)
1.7	43 (35–47)	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)
1.9	44 (36–49)	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)
2.1	45 (37–50)	47 (38–52)	48 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)
2.3	47 (38–52)	49 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)
2.5	49 (40–54)	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)
2.7	50 (41–55)	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)
2.9	52 (42–57)	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)
3.1	53 (44–59)	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)
3.3	55 (45–61)	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)	
3.5	57 (47–63)	59 (48–65)	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)		
3.7	59 (48–65)	61 (50–>65)	63 (53–>65)	65 (53–>65)	>65 (55–>65)			
3.9	61 (50–>65)	63 (51–>65)	65 (53–>65)	>65 (55–>65)				
4.1	63 (51–>65)	65 (53–>65)	>65 (55–>65)					
4.3	65 (53–>65)	>65 (55–>65)						
4.5	>65 (55–>65)							

Tehrani FR et al.:J Clin Endocrinol Metab 98: 729-735, 2013

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Menopausal age prediction with AMH and age

21-46 age 257 patient (11 years)

AMH level (ng/ml)													Percentile AMH	Predicted age at menopause				
														p5	p25	Median	p75	p95
9.78	8.26	6.85	5.77	4.96	4.38	4.02	3.73	3.28	2.56	1.70	1.00	0.54	95	47.7	52.6	55.3	57.5	60.1
6.72	5.68	4.71	3.96	3.41	3.02	2.76	2.56	2.26	1.76	1.17	0.69	0.37	90	47.4	52.3	54.9	57.1	59.7
5.22	4.41	3.66	3.08	2.65	2.34	2.15	1.99	1.75	1.37	0.91	0.53	0.29	85	47.1	51.9	54.5	56.7	59.2
4.27	3.61	2.99	2.52	2.17	1.92	1.76	1.63	1.43	1.12	0.74	0.44	0.24	80	46.7	51.5	54.2	56.3	58.8
3.60	3.04	2.52	2.12	1.82	1.61	1.48	1.37	1.21	0.94	0.63	0.37	0.20	75	46.4	51.2	53.8	55.9	58.4
3.08	2.60	2.16	1.82	1.56	1.38	1.27	1.18	1.03	0.81	0.54	0.31	0.17	70	46.1	50.8	53.4	55.5	58.0
2.67	2.26	1.87	1.57	1.35	1.20	1.10	1.02	0.90	0.70	0.46	0.27	0.15	65	45.8	50.5	53.0	55.1	57.6
2.33	1.97	1.63	1.37	1.18	1.04	0.96	0.89	0.78	0.61	0.41	0.24	0.13	60	45.4	50.1	52.7	54.8	57.2
2.04	1.73	1.43	1.20	1.04	0.92	0.84	0.78	0.69	0.54	0.36	0.21	0.11	55	45.1	49.8	52.3	54.4	56.8
1.79	1.52	1.26	1.06	0.91	0.80	0.74	0.68	0.60	0.47	0.31	0.18	0.10	50	44.8	49.4	51.9	54.0	56.4
1.58	1.33	1.10	0.93	0.80	0.71	0.65	0.60	0.53	0.41	0.27	0.16	0.09	45	44.5	49.1	51.6	53.6	56.0
1.38	1.17	0.97	0.81	0.70	0.62	0.57	0.53	0.46	0.36	0.24	0.14	0.08	40	44.2	48.7	51.2	53.2	55.6
1.21	1.02	0.85	0.71	0.61	0.54	0.50	0.46	0.41	0.32	0.21	0.12	0.07	35	43.9	48.4	50.8	52.9	55.2
1.05	0.88	0.73	0.62	0.53	0.47	0.43	0.40	0.35	0.27	0.18	0.11	0.06	30	43.6	48.0	50.5	52.5	54.8
0.90	0.76	0.63	0.53	0.45	0.40	0.37	0.34	0.30	0.23	0.16	0.09	0.05	25	43.3	47.7	50.1	52.1	54.5
0.75	0.64	0.53	0.44	0.38	0.34	0.31	0.29	0.25	0.20	0.13	0.08	0.04	20	43.0	47.4	49.8	51.8	54.1
0.62	0.52	0.43	0.36	0.31	0.28	0.25	0.24	0.21	0.16	0.11	0.06	0.03	15	42.7	47.0	49.4	51.4	53.7
0.48	0.40	0.34	0.28	0.24	0.21	0.20	0.18	0.16	0.13	0.08	0.05	0.03	10	42.4	46.7	49.1	51.1	53.3
0.33	0.28	0.23	0.19	0.17	0.15	0.14	0.13	0.11	0.09	0.06	0.03	0.02	5	42.1	46.4	48.8	50.7	53.0
Age (yr)	20–22	22–24	24–26	26–28	28–30	30–32	32–34	34–36	36–38	38–40	40–42	42–44	44–46					

Broer SL et al.:J Clin Endocrinol Metab 96: 2532-2539, 2011

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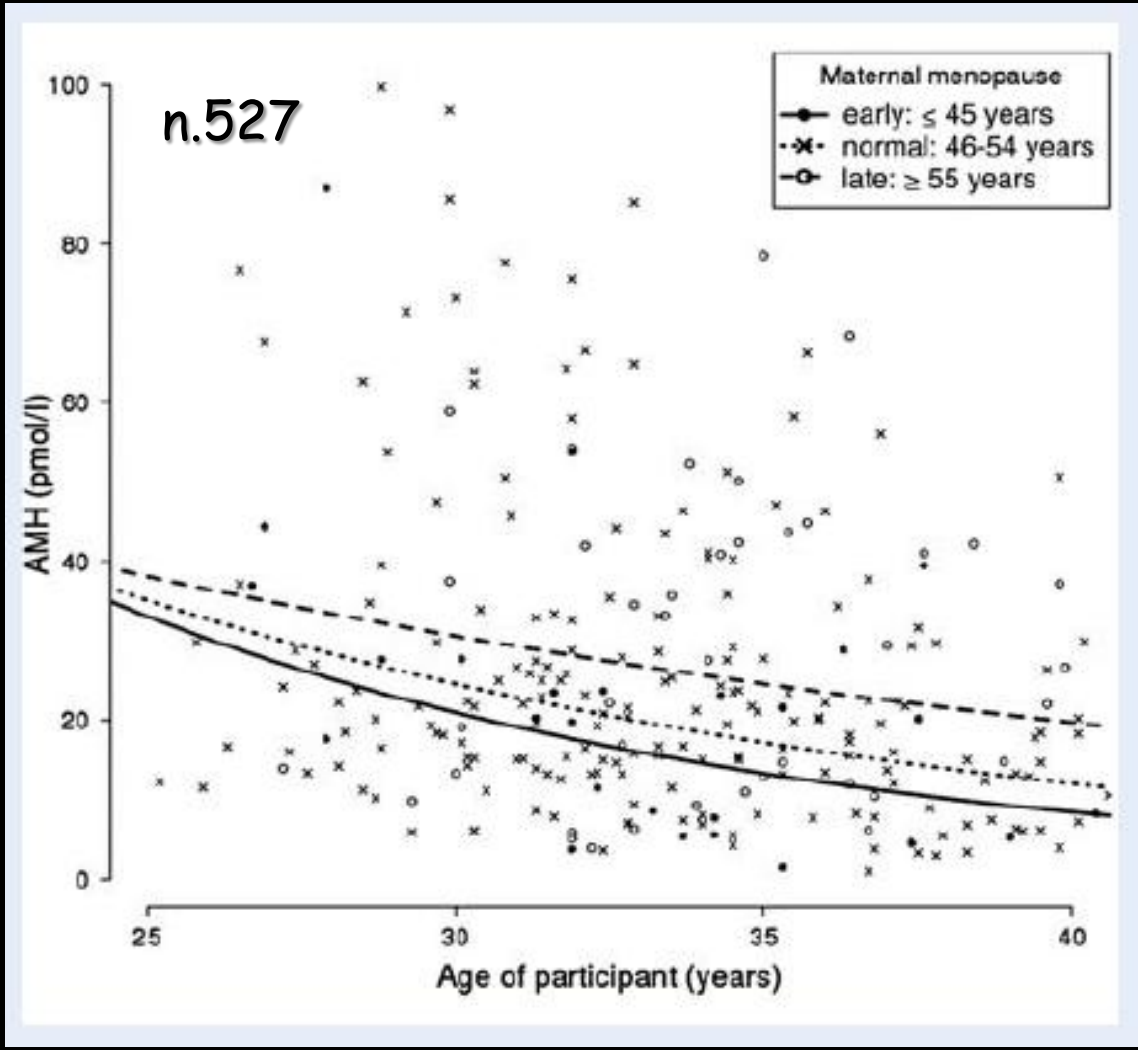
Maternal menopause age and annual decline in daugters AMH levels



Maternal Menopause Age	AMH concentration decline (%)
<45 yaş	8,6
46-54 yaş	6,8
>55 yaş	4,2

Bentzen JG: Human Reproduction, 28,:247-255, 2013

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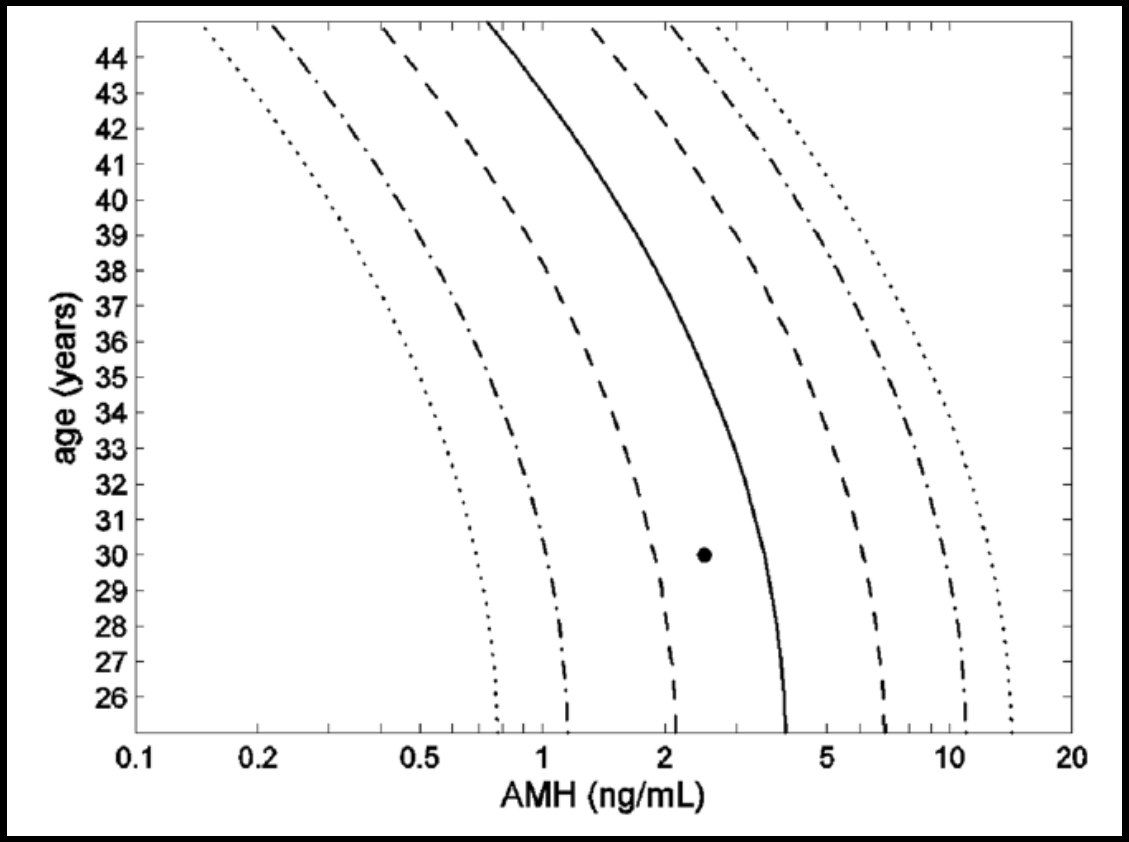


Age-dependent AMH-percentiles

and

Estimated percentiles of the probability distribution of age at menopause

AMH critical threshold	Predicted age at menopause (± standard error)
5°	42.3 (0.2)
10°	44.3 (0.1)
25°	47.1 (0.1)
50°	49.6 (0.1)
75°	51.8 (0.1)
90°	53.8 (0.1)
95°	55 (0.1)

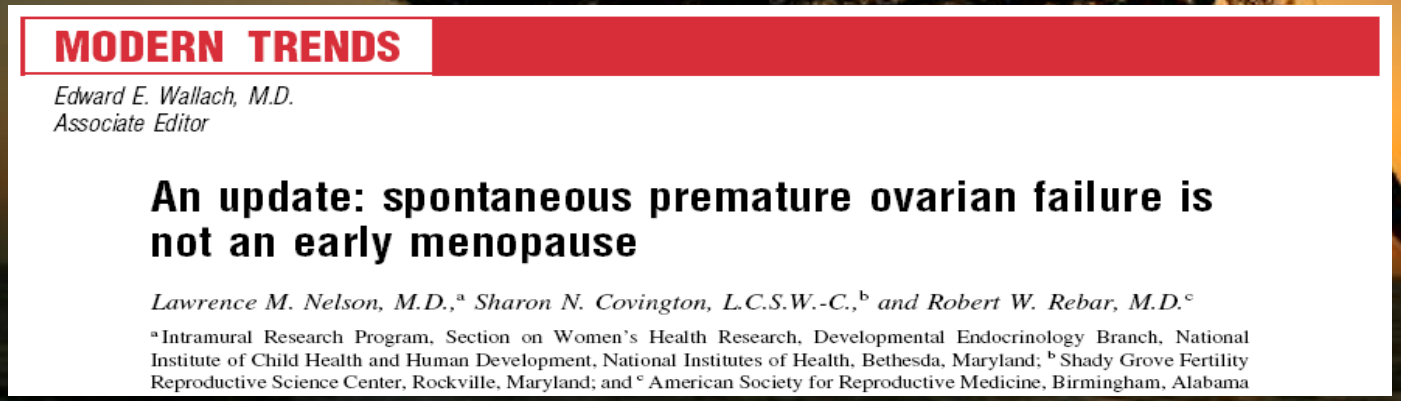
doi:10.1371/journal.pone.0057005.t004

La Marca A, Sighinolfi G, Papaleo E, Cagnacci A, Volpe A, Faddy MJ.:PLOS ONE, 8:1, 2013

POF - Terminology - Insidence

Premature ovarian failure is not early menopause.

Ovarian failure is not irreversible for all patients.



MODERN TRENDS

Edward E. Wallach, M.D.
Associate Editor

An update: spontaneous premature ovarian failure is not an early menopause

Lawrence M. Nelson, M.D.,[a] Sharon N. Covington, L.C.S.W.-C.,[b] and Robert W. Rebar, M.D.[c]

[a] Intramural Research Program, Section on Women's Health Research, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; [b] Shady Grove Fertility Reproductive Science Center, Rockville, Maryland; and [c] American Society for Reproductive Medicine, Birmingham, Alabama

"Premature menopause" should not be used as "premature ovarian failure"

1. Medical failure,
2. Confuse for patient,
3. Harmful for patient psychology.

Nelson LM et al.:Fertil Steril, 83:1327, 2005

SŞ

AMH in POF diagnosis

Table 1. Demographical and clinical parameters regarding for groups.

Variables	Controls (n=89)	Elevated FSH (FSH <40) (n=48)	POF (FSH >40) (n=38)	p-value
Age (years)	30.7±5.5	33.0±5.5	30.4±6.5	0.055
BMI (kg/m^2)	26.4±4.9	27.4±5.7	24.4±3.5	0.208
AMH	2.1 (0.04-11.0)*, †	0.1 (0.01-1.1)*	0.03 (0.01-2.0) †	<0.001
FSH	6.2 (0.1-20.4)*, †	22.2 (10.2-39.0)*, ‡	67.0(41.0-162.0)†, ‡	<0.001
LH	2.9 (0.1-12.7)*, †	6.7 (1.6-24.0)*, ‡	31.5 (8.4-120.0) †, ‡	<0.001
E2	39.0 (9.0-108.0)*, †	22.5 (8.0-130.0)*	16.5 (4.0-110.0) †	<0.001

*: The difference between controls and EFSH groups was statistically significant (p<0.001), †: The difference between control and POF groups was statistically significant (p<0.001), ‡: The difference between EFSH and POF groups was statistically significant (p<0.001).

Sahmay S, Usta T, Erel CT, Atakul N, Aydogan B.: Elevated serum LH levels draw A stronger distinction between premature ovarian failure cases and elevated serum FSH cases than AMH. Climacteric. 2014 Apr;17(2):197-203

SŞ

AMH in POF diagnosis

Table 5. Results of Multiple Logistic Regression Analyses.

Models	OR (95% CI)	p-value	Wald	Sensitivity	Specificity
Control vs EFSH				91.7	93.3
AMH<0.955	62.672 (6.582-596.734)	<0.001	12.952		
FSH>11.8	11.059 (2.236-54.695)	0.003	8.683		
LH>4.35	1.090 (0.203-5.846)	0.920	0.010		
E2<30.5	3.673 (0.814-16.576)	0.091	2.863		
Control vs POF				73.7	95.5
AMH<0.945	46.846 (10.828-202.678)	<0.001	26.496		
E2<28.5	14.803 (3.944-55.566)	<0.001	15.944		
EFSH vs POF				89.5	93.8
LH>16.18	144.712 (26.276-796.985)	<0.001	32.661		
E2<21.5	4.028 (0.717-22.646)	0.114	2.502		

Sahmay S, Usta T, Erel CT, Atakul N, Aydogan B.: Elevated serum LH levels draw A stronger distinction between premature ovarian failure cases and elevated serum FSH cases than AMH. Climacteric. 2014 Apr;17(2):197-203

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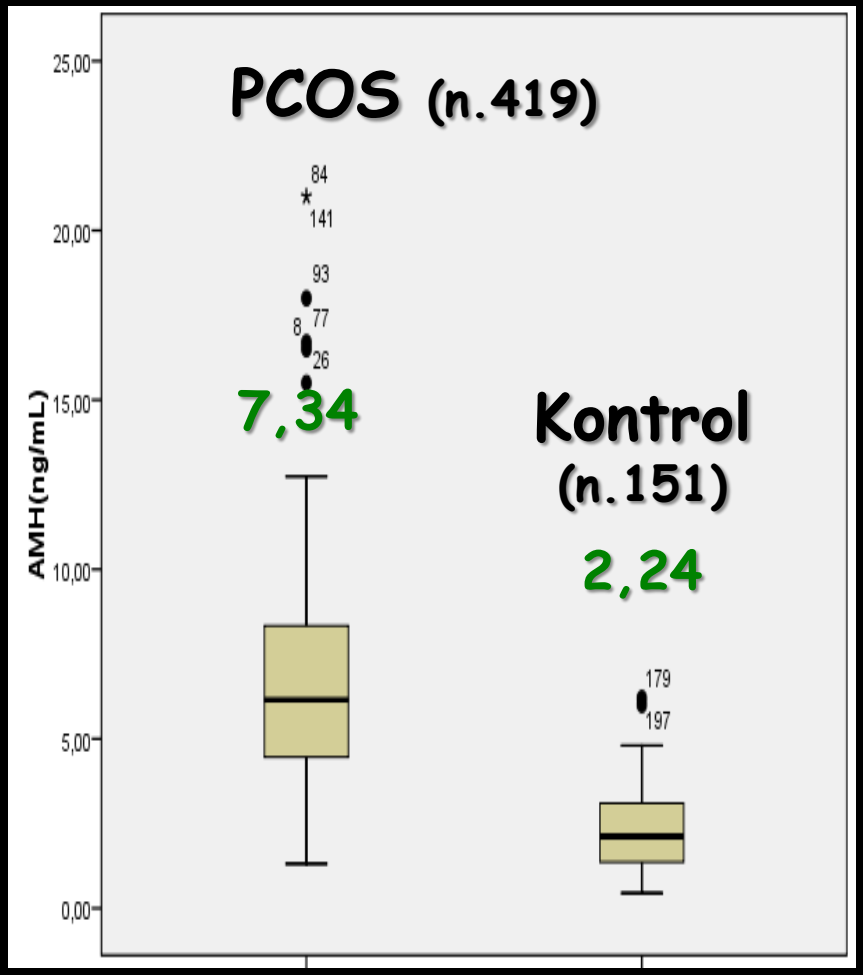
Serum AMH levels in PCOS



Reason of AMH increase in PCOS;

- Excess follicular count
- Increase follicular production

Sahmay S, Atakul N, Aydogan B, Aydın Y, İmamoğlu M, Seyisoğlu H. Acta Obstet Gynecol Scand 2013 Dec;92(12):1369-74

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AMH levels according to age in PCOS - nonPCOS

	Age of PCOS (year)	Age of Control (year)	p (Age)	AMH-PCOS (ng/ml)	AMH-Control (ng/ml)	p (AMH)
35-40 years	36.4±1.6 (n=29)	37.0±1.4 (n=130)	0.06	5.4±2.2	1.7±1.3	0.001
29-34 years	31.1±1.6 (n=99)	31.3±1.6 (n=143)	0.17	6.8±3.4	2.3±1.6	0.001
23-28 years	25.4±1.7 (n=174)	26.1±1.5 (n=83)	0.01*	7.6±4.1	2.7±1.8	0.001
17-22 years	19.4±1.9 (n=117)	19.9±1.3 (n=16)	0.31	7.8±4.5	3.9±2.5	0.001

Sahmay S, Atakul N, Aydogan B, Aydın Y, İmamoğlu M, Seyisoğlu H. Acta Obstet Gynecol Scand 2013 Dec;92(12):1369-74

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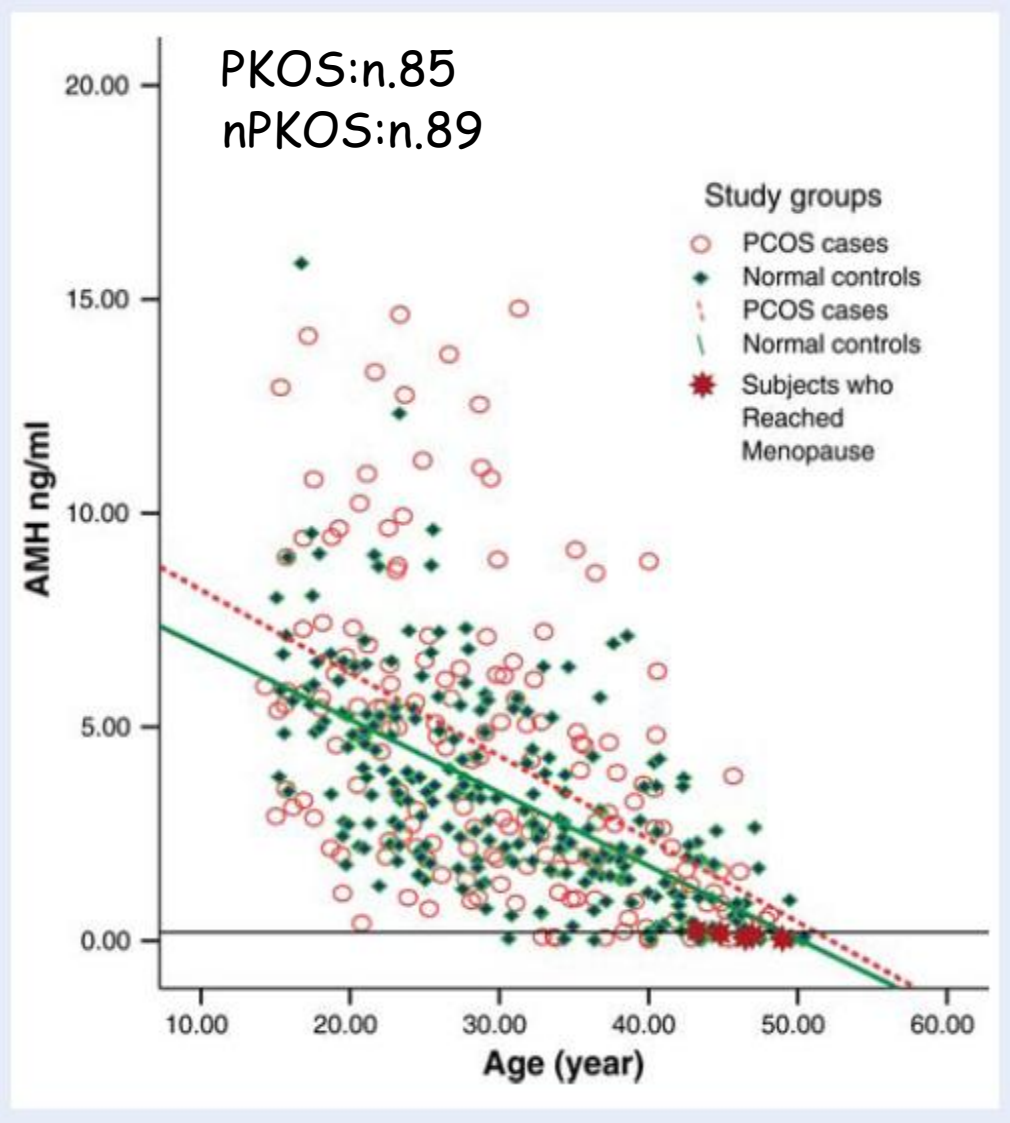
Reproductive life is longer in PCOS



Tehrani FR et al.:Human Reprod 25: 1775–1781, 2010

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Interpretation of AMH values

AMH ng/mL	Clinical meanings
< 0.08	Severe poor ovarian reserve
0.08 - 0.16	Poor ovarian reserve
0.16 - 1.5	Decreased fertility
1.5 – 4.0	Optimal fertility
> 4.0	Consider PCOS / OHSS

Summary

- Clinical diagnosis of menopause is prior to hormonal evaluation .
- Doctors should be careful during the diagnosis of Premature ovarian failure, especially while using `Early Menopause`.
- AMH measurements are hopeful for prediction of menopause.
- Prediction of menopause is powerful in late reproductive life than younger women.
- AMH measurement is not sensitive for detection of lower levels. (lowest level is 0.08ng/ml)
- Spontanous cycles and even pregnancy is possible in undetectable AMH levels.


KÜLTÜR, okumak, anlamak, görebilmek,
görebildiğinden anlam çıkarmak,
ders almak, düşünmek ve zekayı geliştirmektir.
M. K. ATATÜRK
BİR ULUSUN BÜYÜKLÜĞÜ nüfusun çokluğu ile değil,
AKILLI VE ERDEMLİ kişilerin sayısıyla ölçülür.
VICTOR HUGO
Eğer bir ülkede cücelerin gölgeleri
uzamaya başlamışsa güneş batıyor demektir.
ÇİN ATASÖZÜ