Polycystic Ovarian Syndrome – a lifelong disorder ?

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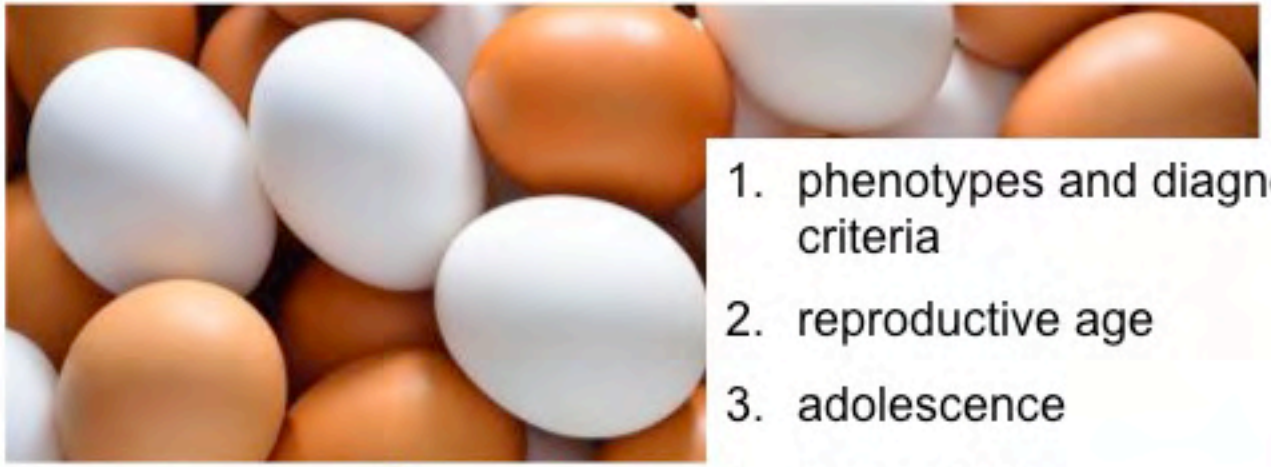
PCOS

- Endocrine, metabolic and reproductive disorder
- 80 % anovulatory infertility
- prevalence of 10 - 15 % during reproductive age
- 70 % insulin resistance
- higher risk of depression and anxiety
- adverse cardiovascular (cv) risk profile
- higher risk of cancer

?



1. phenotypes and diagnostic criteria
2. reproductive age
3. adolescence
4. menopause

Genetics and pathophysiology

- **ovarian and adrenal steroidogenesis**:
CYP11A, CYP17A1, CYP 19, HSD17B1 & HSD17B2, HSD3B1&HSD3B2, StAR

- **steroid hormone action:**
Androgenrezeptor, SHBG

- **action and regulation of gonadotropins:**
LH, FSH, Inhibin βA , Inhibin βB, MADH4

- **insulin action and –secretion:**
Insulin VNTR, IGF-II, insulinreceptor gene, insuline receptor substrate T, PPAR- γ

- **obesitiy und metabolism:**
Leptin, Leptinrezeptor, POMC, UCP2 + 3

Genom Data. 2016 Jun; 8: 52–60.

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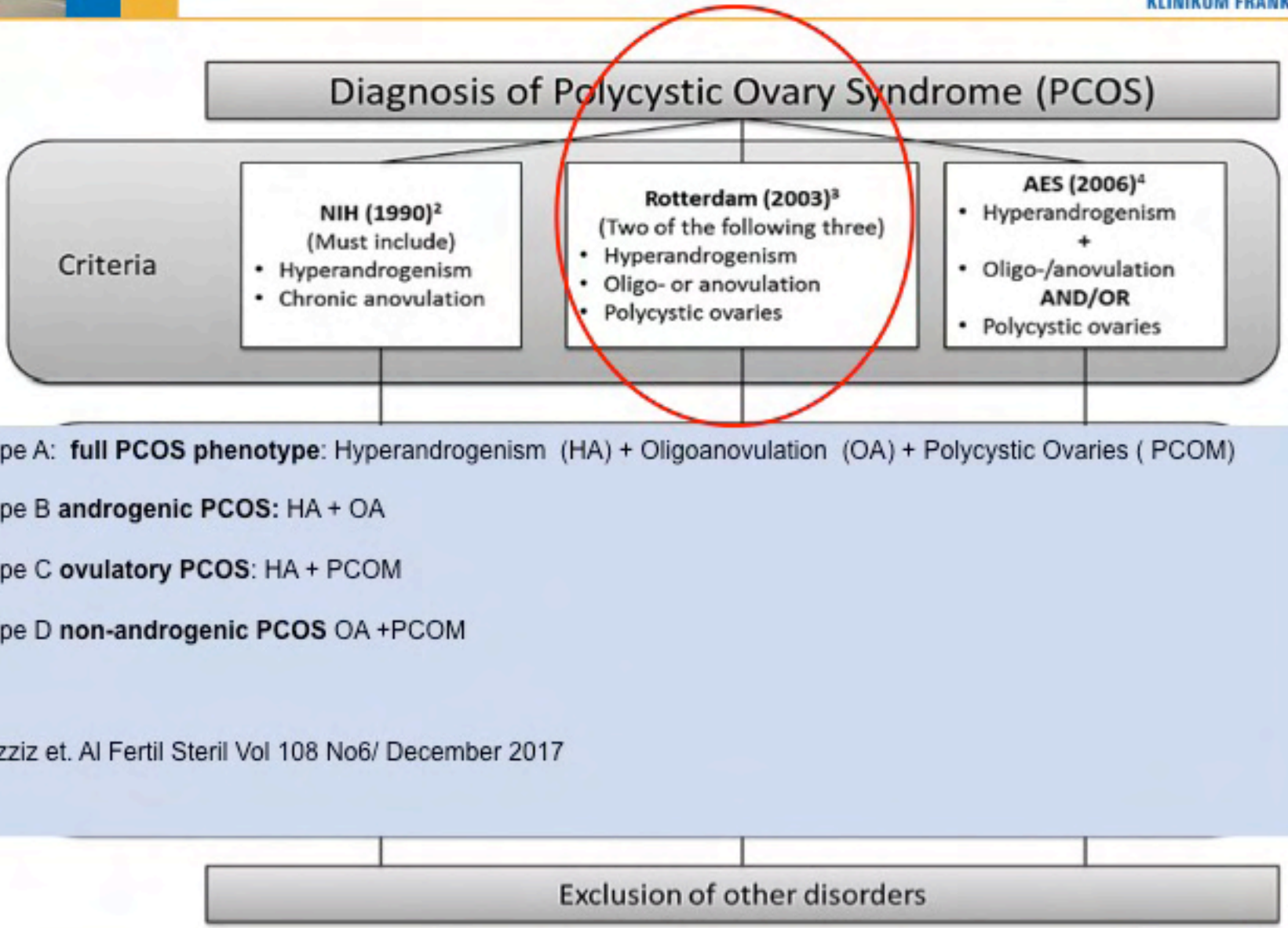
PCOS Phenotypes

TABLE 1

All possible phenotypes based on the presence or absence of oligo anovulation, hyperandrogenemia, hirsutism, and polycystic ovary syndrome (PCOS).

	Potential Phenotypes															
Features	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**
Hyperandrogenemia	+	+	+	+	–	–	+	–	+	–	+	–	–	–	+	–
Hirsutism	+	+	–	–	+	+	+	+	–	–	+	–	–	+	–	–
Oligo-anovulation	+	+	+	+	+	+	–	–	–	+	–	–	+	–	–	–
Polycystic ovaries	+	–	+	–	+	–	+	+	+	+	–	+	–	–	–	–
NIH 1990 criteria	√	√	√	√	√	√										
Rotterdam 2003 criteria	√	√	√	√	√	√	√	√	√	√						
AE-PCOS 2006 criteria	√	√	√	√	√	√	√	√	√							

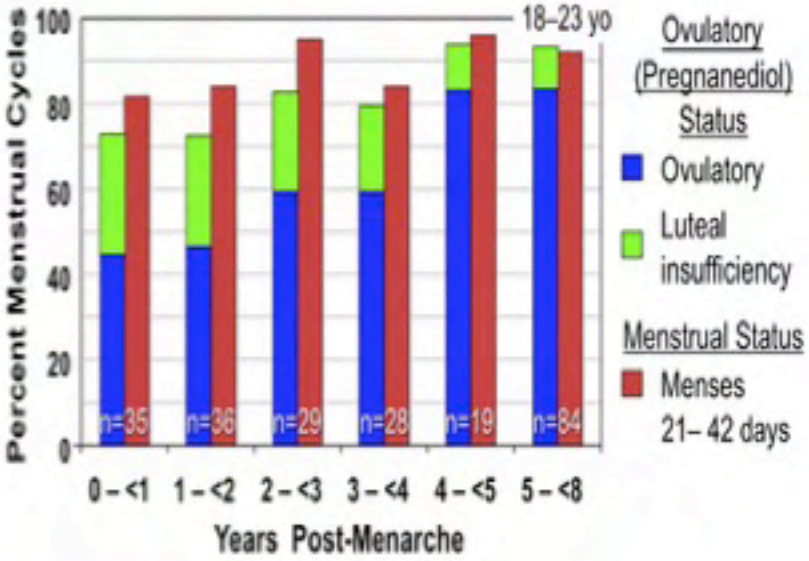
Azziz. AE PCOS Society report on PCOS phenotype. Fertil Steril 2009.


Diagnosis of Polycystic Ovary Syndrome (PCOS)
Criteria
NIH (1990)[2]
(Must include)
• Hyperandrogenism
• Chronic anovulation
Rotterdam (2003)[3]
(Two of the following three)
• Hyperandrogenism
• Oligo- or anovulation
• Polycystic ovaries
AES (2006)[4]
• Hyperandrogenism
+
• Oligo-/anovulation
AND/OR
• Polycystic ovaries
Type A: full PCOS phenotype: Hyperandrogenism (HA) + Oligoanovulation (OA) + Polycystic Ovaries (PCOM)
Type B androgenic PCOS: HA + OA
Type C ovulatory PCOS: HA + PCOM
Type D non-androgenic PCOS OA +PCOM
Azziz et. Al Fertil Steril Vol 108 No6/ December 2017
Exclusion of other disorders

PCOS during reproductive age

1. Anovulatory infertility
2. Menstrual disorders
3. Clinical signs of hyperandrogenism

PCOS in adolescents



primary amenorrhea	Lack of menarche by 15 y of age or by 3 years after the onset of breast development[a]
secondary amenorrhea	Over 90 d without a menstrual period after initially menstruating
oligomenorrhea (infrequent AUB)	Postmenarcheal year 1: average cycle length >90 d (<4 periods/y)
	Postmenarcheal year 2: average cycle length >60 d (<6 periods/y)
	Postmenarcheal years 3–5: average cycle length >45 d (<8 periods/y)
	Postmenarcheal years ≥6: cycle length >38–40 d (≤9 periods/y)
Excessive anovulatory AUB†	Menstrual bleeding that occurs more frequently than every 21 d (19 d in yr 1) or is excessive (lasts >7 d or soaks >1 pad or tampon every 1–2 h)

Rosenfield et al. Pediatrics 2015;136:1154-1165

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PCOS in adolescents

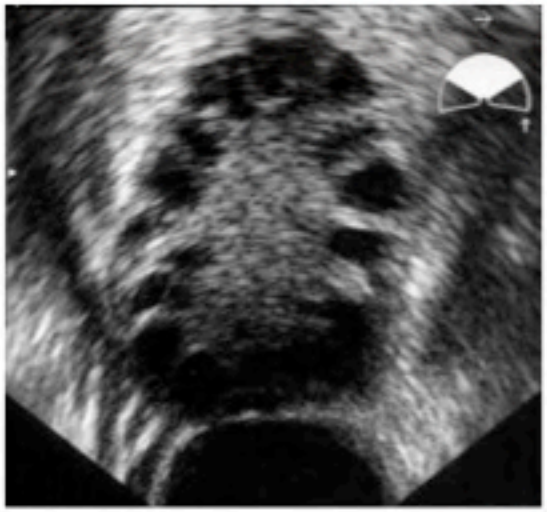
Diagnostic criteria

- Otherwise unexplained **persistent hyperandrogenic anovulation for > 2 years** after menarche (Rosenfield et al 2015)
- 2012 ESHRE/ASRM criteria Workshop Group: **all 3 Rotterdam 2003 criteria** (Carmina et al. 2010
- clinical hyperandrogenism, oligomenorrhea or amenorrhea at least two years post menarche, biologic hyperandrogenism, **insulin resistance**, and polycystic ovarian morphology (Sultan and Paris, 2006; Fauser et al., 2012)

- What is normal and which features have an impact for the rest of a young girls life?

Rosenfield et al.Pediatrics. 2015 Dec;136(6):1154-65.
Good-man N.F et al. En-do-crine Prac-tice Vol 21 No. 11 No-vem-ber 2015, pp 1291-1300.
Fauser et al. Fertil Steril. 2012;97(1):28–38

Ultrasound criteria



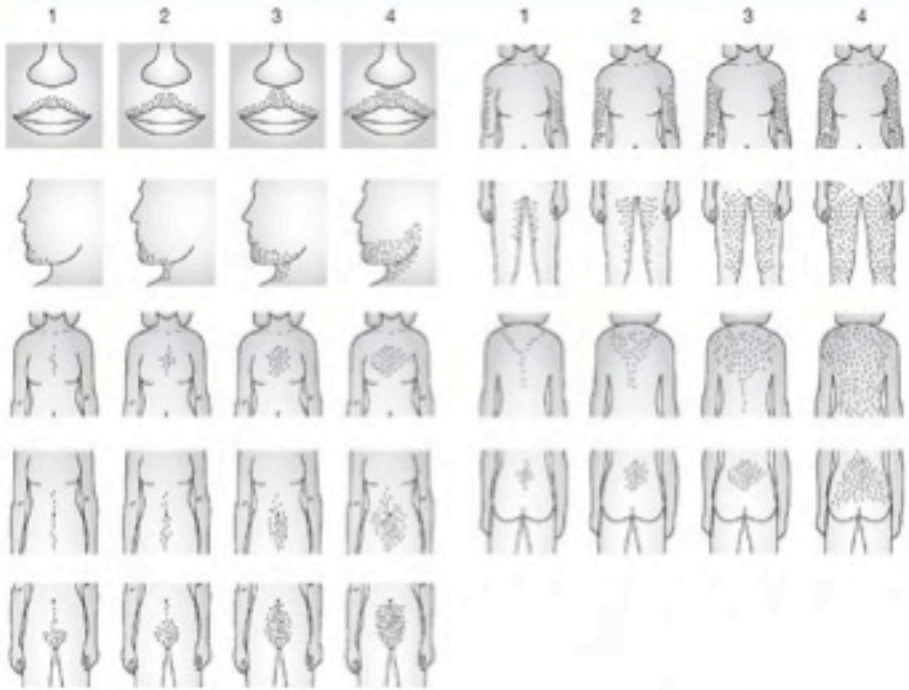
adolescents:
the diagnosis of polycystic ovaries on ultrasound should include increased ovarian size (>10 cm^3)

reproductive age:
Until 2015: 12 AF
Now: at least 25 AF of 2-9 mm

postmenopausal:
n.a.

Balen AH, et al.. Hum Reprod Update. 2003 Nov-Dec;9 (6):505-14.
Goodman NF, et al. Endocr Pract. 2015 Nov;21(11):1291-300

Clinical signs of Hyperandrogenaemia



- subjective
- less prevalent in adolescents, develops over time
- In adolescents hyperandrogenemia rather than just signs of androgen excess should be documented

Modified Ferriman–Gallwey scoring System for Hirsutism for all age groups.

9 areas
0 = no terminalhair
4 = extensive growth of terminal hair
6-8 = hirsutism

Hyperandrogenaemia

Free testosterone and SHBG

- poor precision in the low menopausal range

AMH-Assays

- American Association of Clinical Endocrinologists (AAC) cut off 4,9 ng/ml
- missing standards

PCOS in perimenopausal and menopausal women

- no diagnostic criteria
- diagnosis of PCOS can be based on a well-documented long-term history of oligomenorrhea and hyperandrogenism during reproductive years.
- patient cohorts are often recruited long before the Rotterdam PCOS consensus
- vague criteria such as past menstrual irregularities.
- statistical predicitions

Legro et al. J Clin Endocrinology & Metabolism, Volume 98, Issue 12, 1 December 2013, Pages 4565–4592

Age at menopause

Findings in fractional polynomial regression model:

- The serum concentration of AMH among 378 PCOS-participants (Rotterdam criteria) was significantly higher than in 784 controls (5.4 ng/ml (IQR 2.8-9.1 ng/ml) vs. 1.4 ng/ml (IQR 0.6-2.7 ng/ml), $p < 0.001$).
- The estimated mean age at menopause was 51.4 (95% CI 45-59) years and 49.7 (95% CI 45-55) years in PCOS cases and healthy controls, respectively.

Confounding Problems:

- Only reproductive aged women were examined (28.3 ± 5.02 vs. 36.02 ± 6.4 years)
- It is only a prediction

Minooee S[1] et al, Climacteric. 2018 Feb;21(1):29-34,

Clinical findings in postmenopausal PCOS

- 25 PCOS patients (histopathological diagnosis of Stein-Leventhal-Syndrome) 68 controls
- **No difference** in menopausal age, body weight, body mass index, waist to hip ratio, LH, prolactin, androstenedione, dehydroepiandrosterone sulfate, total testosterone, estradiol, and estrone established premenopausal
- increase in waist to hip ratio in PCOS patients **disappeared** after menopause, mainly due to weight gain among controls.
- PCOS women had **higher free androgen index** ($P = 0.001$) but lower FSH ($P < 0.001$) and SHBG ($P < 0.01$) than controls. .
- Women with PCOS reported hirsutism more frequently ($P < 0.001$) but
- had **fewer climacteric symptoms** ($P < 0.05$) and hypothyroidism than controls ($P < 0.05$).

Schmidt, et al. *J of Clinical Endocrinology & Metabolism*, Vol. 96, Issue 7, 1 July 2011

Climacteric symptoms

- **Midlife Women's Health Study** involving 780 women aged 45 to 54 years. 9.3% (n=42) with history of PCOS based on Rotterdam criteria; 411 controls.
- Mean age was 48.0 and body mass index was 27.3 for women with PCOS.
- There was no difference between PCOS and control women for levels of follicle-stimulating hormone, testosterone, progesterone, or estradiol.
- PCOS not associated with increased odds of hot flash incidence.

Yin et al. Menopause. 2018 Jan 22.

Cardiovascular risk

- PCOS at any age is characterized by greater odds for elevated CVD risk markers
- Dyslipidemia, IGT, and T2D are more prevalent in women with PCOS, even when weight matched with normal control women (level B).
- Altered levels of triglycerides, HDL, LDL, and non-HDL (reflecting altered ApoB/ApoA metabolism) are prevalent in women with PCOS and are **more severe in hyperandrogenic women** (level B).
- Altered Lipoprotein a (LPa), CRP, TNF a, IL6, BNP, ADMA, miRNA 21, miRNA 126, miRNA-145-5p, und der miRNA 17/92a cluster (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a).....

Fauser et al. Fertil Steril. 2012;97(1):28–38.
Escobar-Morreale et al. Fertil Steril. 2011 Mar 1; 95(3): 1048–58.

Recommendations for CVD risk assessment

- Die ESHRE/ASRM-sponsored 3rd PCOS Consensus Workshop Group recommends CVD risk assessment **at any age** for psychosocial stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL, and non-HDL cholesterol), waist circumference, physical activity, nutrition, and smoking (level C).

  (Fauser et al. 2012)

- Endocrine Society: Adolescents and women with PCOS be screened for family history of early cardiovascular disease, cigarette smoking, IGT/T2DM, hypertension, dyslipidemia, OSA, and obesity (especially increased abdominal adiposity)

Fauser et al. Fertil Steril. 2012;97(1):28–38
Legro et al. J Clin Endocrinol Metab. 2013 Dec; 98(12):4565-92.

Stratification of cardiovaskular risk

Stratification of cardiovascular risk in patients according to the current clinical practice guideline for PCOS of the Endocrine Society.

PCOS Patients with high risk for cardiovascular disease	PCOS patients at risk for cardiovascular disease
Metabolic syndrome	Obesity (especially increased abdominal adiposity)
T2DM	Cigarette smoking
Overt vascular or renal disease	Hypertension
Obstructive sleep apnea	Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
	Impaired glucose tolerance
	Family history of premature cardiovascular disease (<55 y of age in male relative; <65 y of age in female relative)

Legro et al. J Clin Endocrinol Metab. 2013 Dec;98(12)

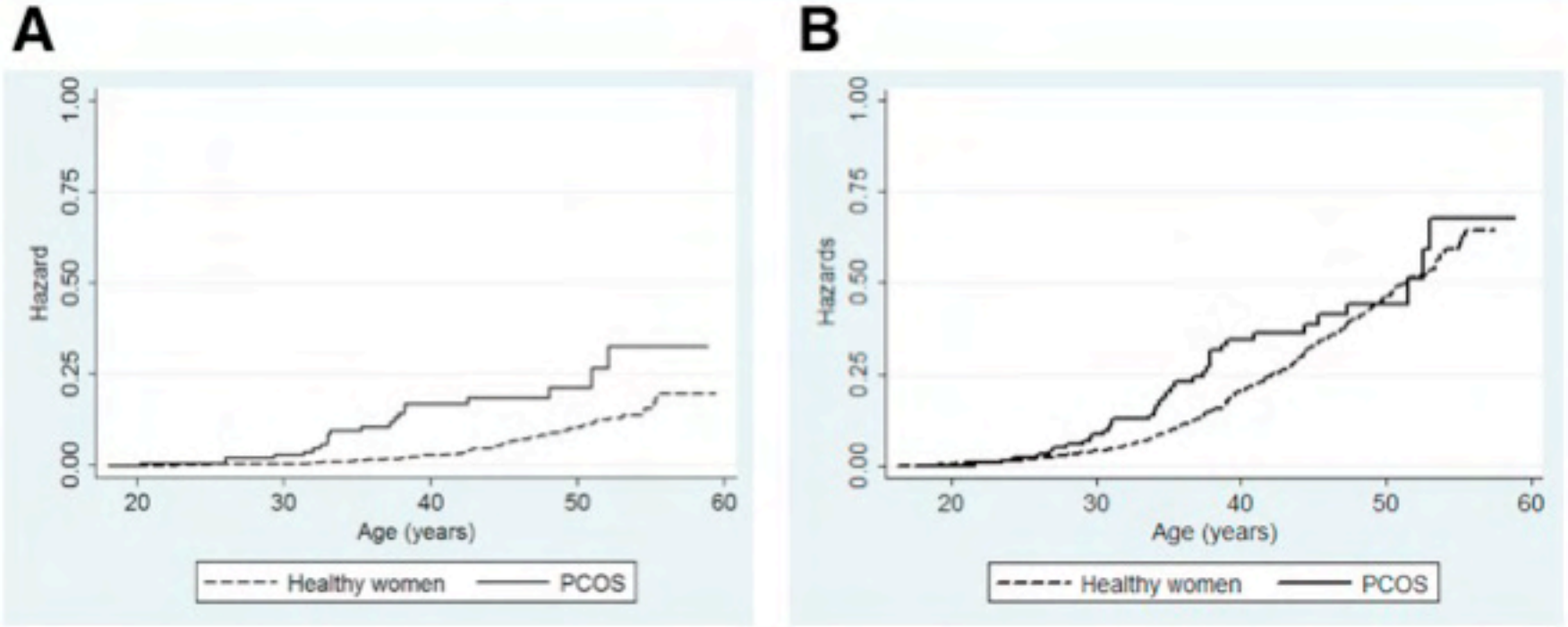
How does risk for T2D develop with age in PCOS ?

Tehran Lipid and Glucose Study, long-term, prospective, population-based study of a cohort of women with PCOS and controls since 1998:

- 178 PCOS Pat., 1524 controls, median follow up 12,9 years
- NIH 1990 criteria: must include hyperandrogenism and oligo-anovulation, i.e. type A full PCOS or type B androgenic PCOS
- mean BMI of the PCOS women studied did not differ from the women without PCOS in this study

Kazemi Jaliseh et al. Fertil Steril. 2017; 108: 1078–1084
Azziz. et al.Fertil Steril, VOL.108 NO.6/ December 2017

Tehran Lipid and Glucose Study



Kaplan-Meier hazard estimates in incidence rates in women with polycystic ovary syndrome and healthy women. Age is used as the time scale. (**A**) Women with diabetes. (Log-rank test, *P*=.001.) (**B**) Women with prediabetes. (Log-rank test, *P*=.057.)

Kazemi Jaliseh et al. Fertil Steril. 2017; 108: 1078–1084

Tehran Lipid and Glucose Study

	PCOS (n = 178)		Healthy women (n = 1,524)		Unadjusted		Multiple adjusted	
Outcome	Yes	No	Yes	No	HR (95% CI)	*P* value	HR (95% CI)[a]	*P* value
Diabetes	21	132	76	1,240				
≤40 y	17	78	27	571	6.6 (3.6–12.2)	.001	4.9 (2.5–9.3)	.001
>40 y	4	54	49	669	1.0 (0.3–2.8)	.953	0.8 (0.3–2.3)	.737
Prediabetes	37	92	317	846				
≤40 y	30	59	175	472	1.9 (1.3–2.8)	.001	1.7 (1.1–2.6)	.005
>40 y	7	33	142	374	0.6 (0.1–1.35)	.240	0.5 (0.2–1.2)	.174

Kazemi Jaliseh et al. Fertil Steril. 2017; 108: 1078–1084

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How does cv-risk develop with age in PCOS ?

- Dahlgren et al 1992 , risk factor model, 33 women with PCOS and 132 age matched references:Considerably increased risk (relative risk of 7.4) of developing myocardial infarction

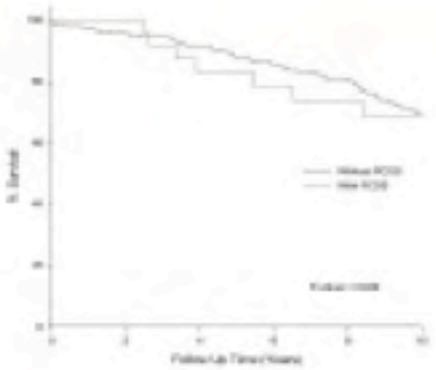
- Meun et al. 2018 **The Roterdam Study:** Linear, logistic, and cox regression models, 2578 women aged over 55:

Postmenopausal high androgen levels were not associated with an increased risk for CVD.

Dahlgren et al. Acta Obstet Gynecol Scand. 992 Dec;71(8):599-604
Meun et al, J Clin Endocrinol Metab. 2018 Feb 1

Women's Ischemia Syndrome Evalutation (WISE) study

- (25/ 295) 8% postmenopausal PCOS
- premenopausal history of irregular menses and current biochemical evidence of hyperandrogenemia,
- trend towards more evidence of angiographic coronary artery disease than women without these features
- raw mortality rates were 28% for women with clinical features of PCOS vs 27% for women without PCOS
- 20% versus 17% for CV-associated deaths.
- Overall, PCOS was not a significant predictor of all-cause or CV mortality rates



Shaw et al. J Clin Endocrinol Metab 2008;93:1276–1284 Retracted
Merz et al. J Womens Health (Larchmt). 2016; 25: 875–881

Further research

CARDIA (Coronary Artery Risk Development in Young Adults) multisite prospective study of 5,115 black and white adults, aged 18-30 years at baseline (1985-86): PCOS= Oligomenorrhea and hyperandrogenism

Funding by the NIH for PCOS, RA, TB, and SLE research for the years 2006 to 2015:

total mean 10-year funding: $215.12 million vs $454.39 million, $773.77 million, and $609.52 million

Wang ET et al . J Clin Endocrinol Metab. 2012 Dec;97(12):4656-62
Bratka et al. J Clin Endocrinol Metab. 2017 Dec 1;102(12):4421-4427

PCOS and cancer

Significantly elevated risk for endometrial cancer:

- Metaanalysis 2014: 919 PCOS, 72054 N-PCOS: OR 2.79; 95% confidence interval (CI), 1.31–5.95, $P < 0.008$).
- **For patients < 54 years:** OR, 4.05; 95% CI, 2.42–6.76, $P < 0.00001$

Conflicting evidence for ovarian cancer:

- Significant for pat ≤ 54 years (OR, 2.52; 95% CI, 1.08–5.89) (Barry et al 2014)
- only Bordeline tumors in obese patients without COC (Harris et al 2017)

Breast cancer not statistically significant

- (OR, 0.95; 95% CI, 0.64–1.39, $P < 0.78$ (Barry et al. 2014)

Barry J.A, et al, Hum Reprod Update. 2014 Sep; 20(5): 748–758
Harris HR et al. Int J Cancer. 2017;140(2):285-291

Summary

- high prevalence
- complex, genetic, endocrine, metabolic and reproductive disorder
- uncertainty about phenotypes in adolescence
- even less is known about PCOS in (peri)menopausal women and its implications on long term health later in life
- significantly higher risk of T2D and endometrial cancer especially during reproductive age
- negative effects might fade with age...
- good medical history and clinical examination, especially of young, reproductive aged patients is crucial....

Thank you!

more well designed prospective long term studies are needed !

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