# PCOS and cardiovascular disease

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**SNUH**

# Polycystic ovary syndrome (PCOS)

- Common endocrine disorder of <u>reproductive</u> women (10-15%).
- Core symptoms are menstrual irregularity and hyperandrogenism such as acne and hirsutism.
  - These symptoms appear since young age and are the primary focus of clinical management.
- Infertility, which is associated with chronic anovulation, is also prevalent in women with PCOS.

# Diagnosis: 2 of the 3 (2003 Rotterdam criteria)



**Polycystic Ovaries**

**Androgen Excess**
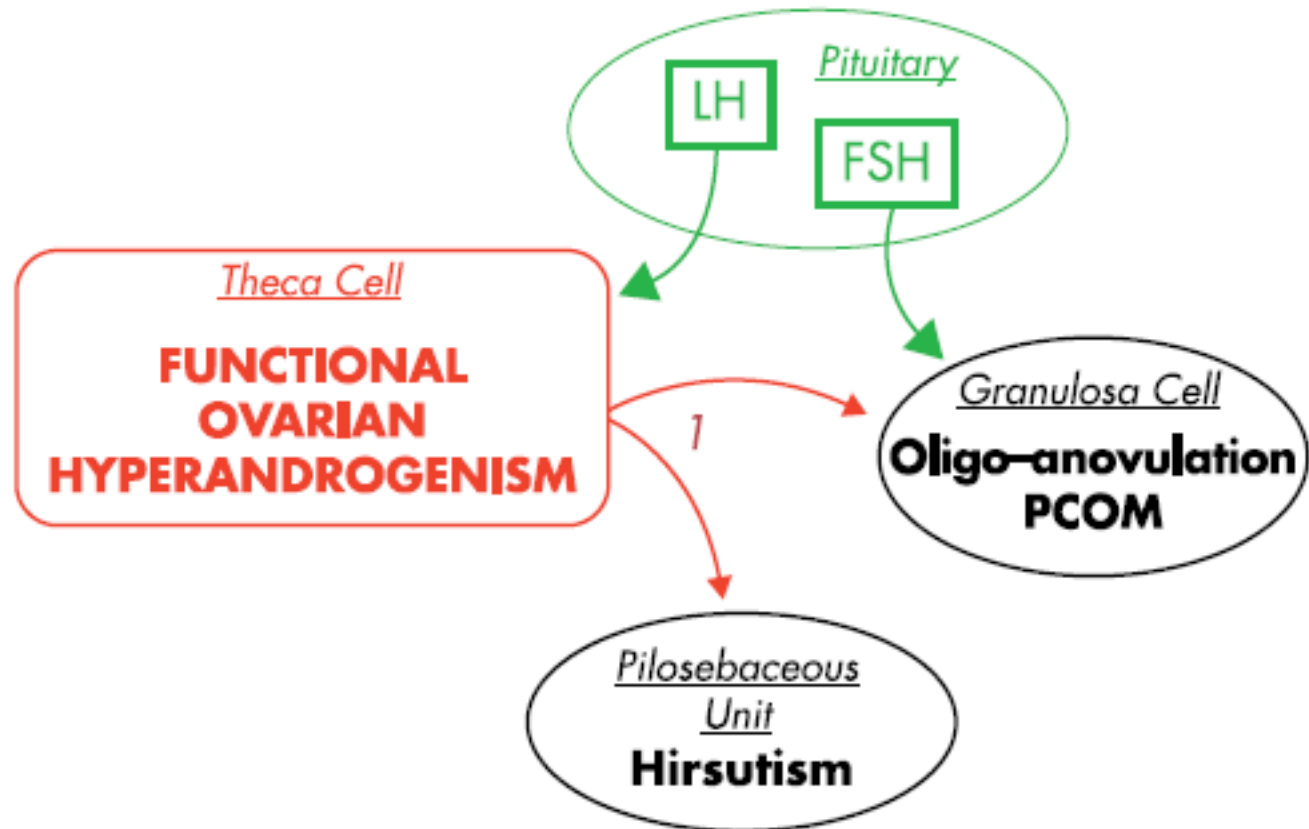
**Anovulation**

1990 NIH criteria
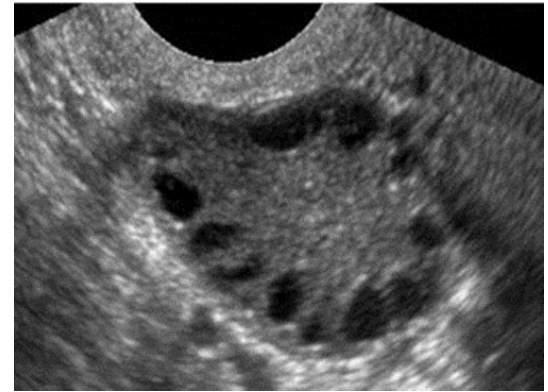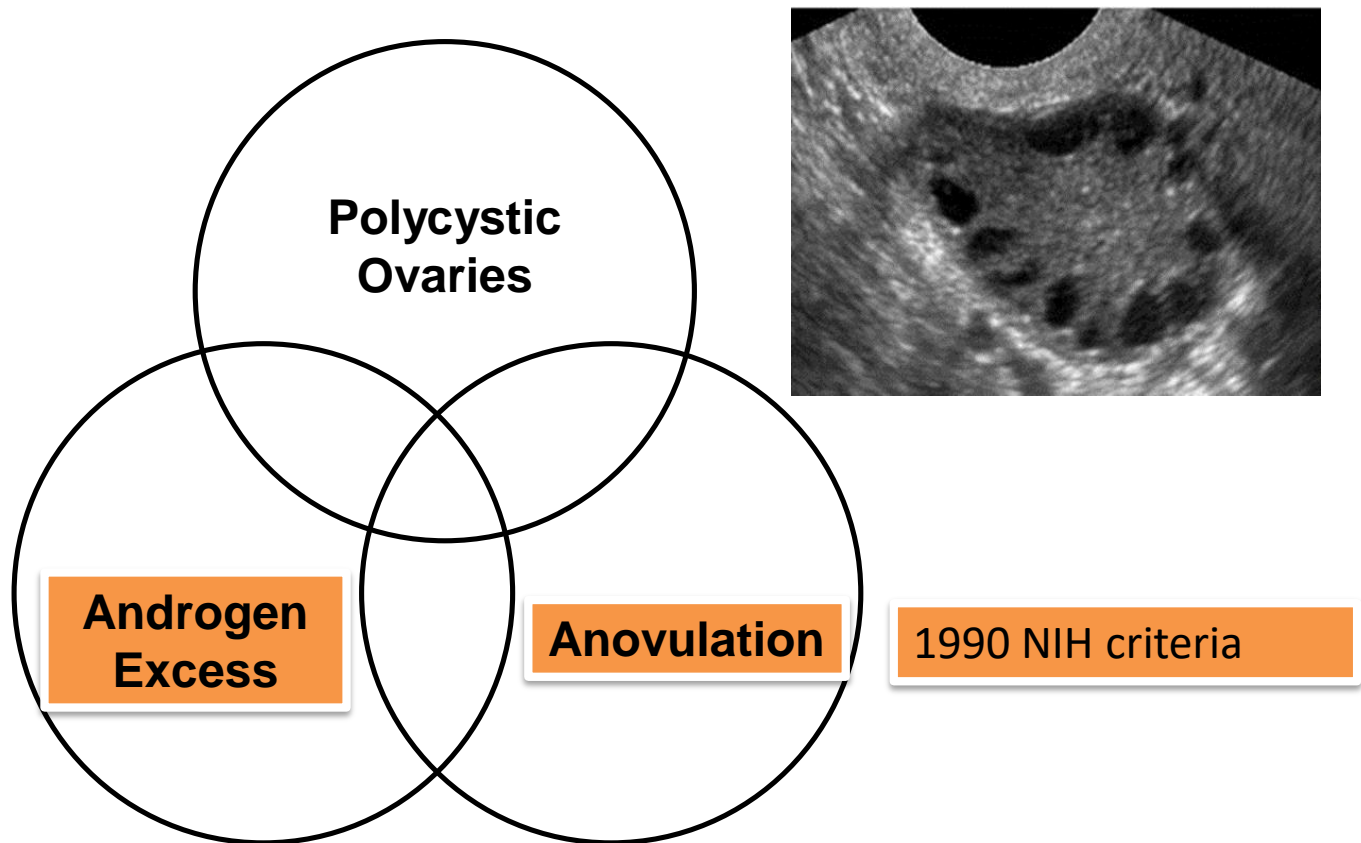
Elevated serum testosterone

- Less than 8 periods per year or cycles > 35 days
- Amenorrhea: absence of menstruation for more than 3 months

# PCOS pathophysiology (1)

Augmented androgen production in ovary is nearly universal.

# PCOS pathophysiology (2)

- From the 1990s, it has been known that insulin resistance and obesity are common in women with PCOS.
- The compensatory hyperinsulinemia has tissue-selective effects, which stimulates ovarian theca cells to secrete testosterone.
- Ovarian hyperandrogenism and insulin resistance seems to be intrinsic.



*Rosenfield and Ehrmann, Endocr Rev 2016*
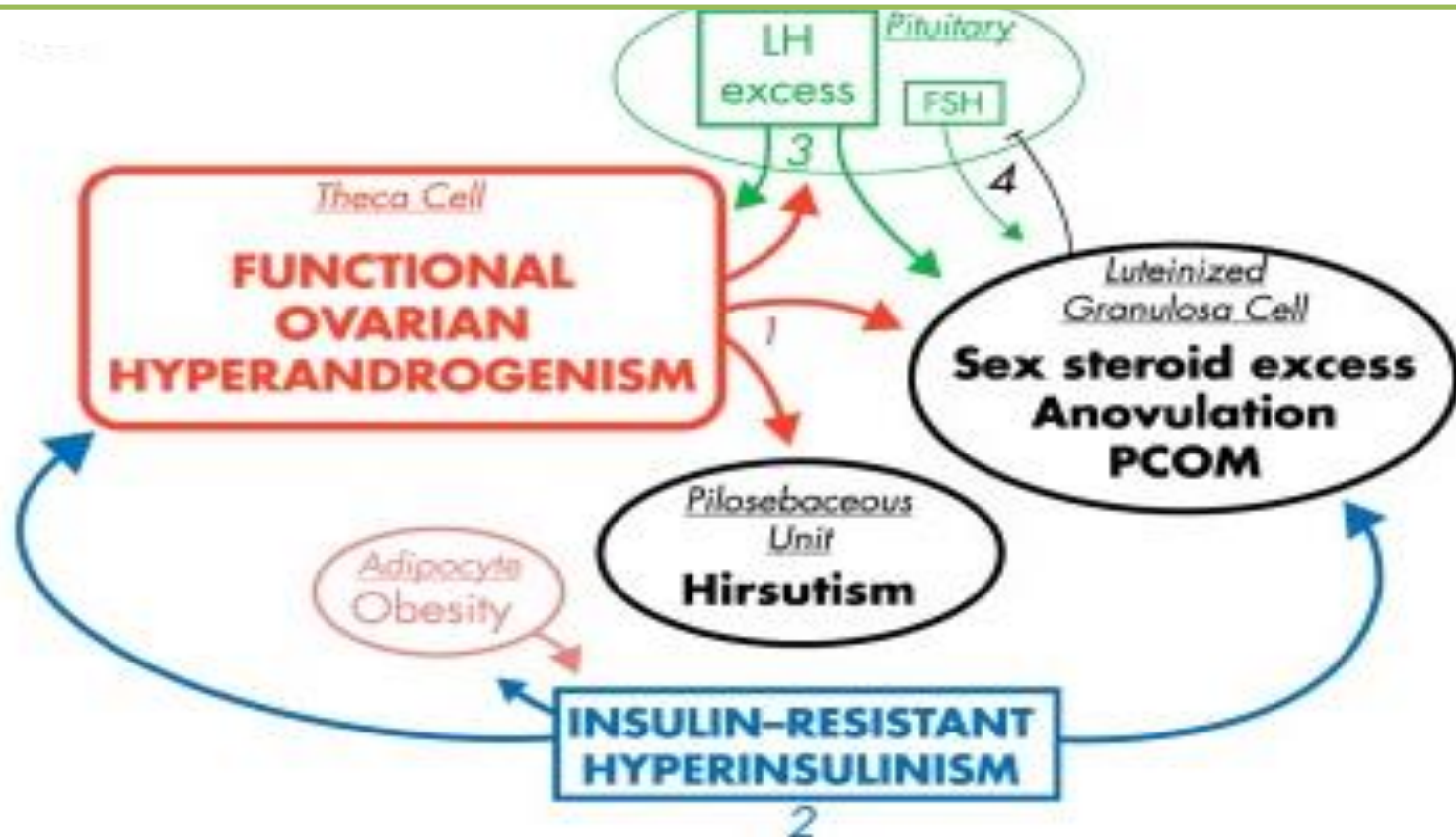
# PCOS pathophysiology (3)

- Although insulin resistance is not part of the diagnostic criteria, it is highly prevalent.
  - 95% of obese patients and 75% of lean patients on euglycaemic-hyperinsulinaemic clamp test (Australia)
  - The optimal HOMA-IR for the diagnosis of metabolic syndrome was 2.64; 34.8% of patients with PCOS had evidence of IR (Korea).
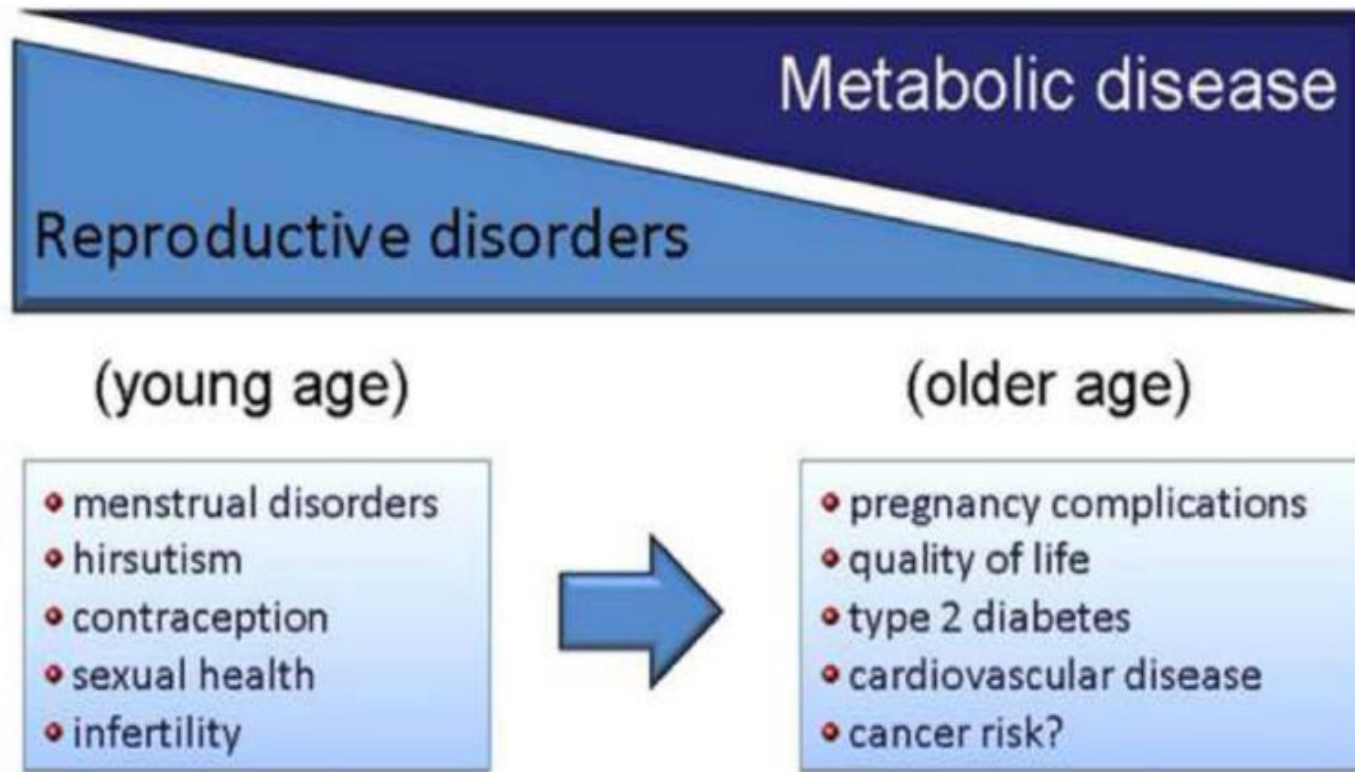
**Prevalence of insulin resistance in Korean women with polycystic ovary syndrome according to various homeostasis model assessment for insulin resistance cutoff values.**

Kim JJ[1], Hwang KR[2], Oh SH[3], Chae SJ[4], Yoon SH[5], Choi YM[6].

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Septo et al. Human Reprod 2013; 28; 777-84; Kim et al., Fertil Steril 2019; 112: 959-66

# Clinical manifestations across the life course : paradigm shift

# PCOS and CVD risk factors

- Women with PCOS have an increased prevalence of CVD risk factors, mediated mostly by insulin resistance, obesity as well as hormonal processes.
  - Dyslipidemia
  - Hypertension
  - Glucose intolerance and diabetes
  - Metabolic syndrome

# CVD risk factors in Korean patients

## Complete phenotypic and metabolic profiles of a large consecutive cohort of untreated Korean women with polycystic ovary syndrome

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865 women with PCOS were consecutively recruited at 13 centers to investigate the complete metabolic and phenotypic profiles of Korean women with PCOS

*Kim et al., Fertil Steril 2014*

## Demographic features of the patients with PCOS.

| | PCOS (all, n = 865) |
|---|---|
| Age, mean ± SD | 24.9 ± 6.0 |
| BMI, kg/m$^2$, mean ± SD | 22.4 ± 4.1 |
| Waist circumference, cm, mean ± SD | 76.8 ± 11.9 |
| Median menstruation cycle, days, median (range) | 60 (4–720) |
| Median no. of cycles per year, median (range) | 6 (0–15) |
| Married, % | 52.7 (456/865) |
| Self-reported reason for visiting hospital, % | |
|   Married subjects | |
|     Infertility with oligo- or amenorrhea | 65.8 (300/456) |
|     Infertility only | 14.0 (64/456) |
|     Oligo- or amenorrhea only | 13.2 (60/456) |
|     Prolonged vaginal bleeding | 5.7 (26/456) |
|     HA symptoms only | 0.2 (1/456) |
|   Unmarried subjects | |
|     Oligo- or amenorrhea only | 69.2 (283/409) |
|     Prolonged vaginal bleeding | 23.7 (97/409) |
|     Oligo- or amenorrhea and HA symptoms | 3.9 (16/409) |
|     HA symptoms only | 1.5 (6/409) |

## PCOS (all, n = 865)

| | PCOS (all, n = 865) |
|---|---|
| Dyslipidemia, % | 35.7 (309/865) |
| Glucose metabolism, % | |
|    Prediabetes | 20.8 (180/851) |
|    Diabetes | 3.5 (30/851) |
| Blood pressure, % | |
|    Prehypertension | 26.2 (227/865) |
|    Hypertension | 4.0 (35/865) |
| General obesity, % | |
|    Overweight | 14.1 (122/865) |
|    Obese | 20.1 (174/865) |
| Central obesity | 33.2 (287/865) |
| Metabolic syndrome | 13.7 (115/839) |

0.2% in 15,005 Korean women (20-29 years)

As high as 80% in USA study

1.42% in 277 Korean women without PCOS (mean 28.3 years)

# PCOS and subclinical CVD

- Women with PCOS have a higher prevalence of subclinical CVD markers.
  - Coronary artery calcium
  - Carotid intima-media thickness
  - Serum CRP, homocysteine
  - Plasminogen activator inhibitor-1, vascular endothelial growth factor, endothelin-1, asymmetric dimethylarginine, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule, advanced glycation end products
  - Flow-mediated dilatation on the brachial artery

# PCOS and CVD event: conflicting (1)

- Meta (2017) (9 cohort studies of 237,647 subjects aged 36–71 years, follow-up 10– 40 years)
  - PCOS was associated with an increased risk of stroke [OR= 1.36 (1.09-1.70)].
  - Not significant after adjustment for BMI [or 1.24 (0.98–1.59)]

- Meta (2016) (case-control and cohort studies of over 100,000 women aged 20–74 years, 7–40 year follow-up)
  - No significant association between PCOS and MI [OR 1.01 (0.68–1.51)]

*Zhao et al. Oncotarget 2016; Zhou et al. Gynecol Endocrinol 2017*

# PCOS and CVD event: conflicting (2)

- Large national registry study in Denmark
  - Median age of 29, followed for a median of 11 years
  - CVD event rates were 22.6 vs. 13.2 per 1000 patient-years for women with PCOS vs. controls [adjusted HR **1.6** (1.5- 1.6)]

- Population-based retrospective study of 2,566 Australian women with PCOS and 25,660 randomly selected age-matched controls
  - The adjusted HR for ischemic heart disease, cerebrovascular disease, arterial/venous disease were **2.89** (1.68–4.97), **2.58** (1.43–4.67) and **1.81** (1.59–2.05).

*Glintborg et al. Cardiovasc Diabetol 2018; Hart et al. J Clin Endocrinol Metab 2015*

# PCOS and CVD event: conflicting (3)

- Meta-analysis (2019) (16 studies including 12 population-based)
  - HR of CVD events increased <u>only in reproductive aged patients</u> [1.43, (1.27, 1.61)], not menopausal patients.
  - History of PCOS during reproductive ages may not be an important risk factor for developing events in later life.

*Tehrani et al. Gynecol Endocrinol 2019*

# Inconsistent findings

- Longitudinal studies of well-defined cohorts are limited.
  - Existing cohorts have poorly defined PCOS status and focus on younger women, or on CVD risk factors rather than clinical events.
- CVD primarily affects postmenopausal women in the later decades of life
  - Difficult in diagnosing PCOS after the menopause
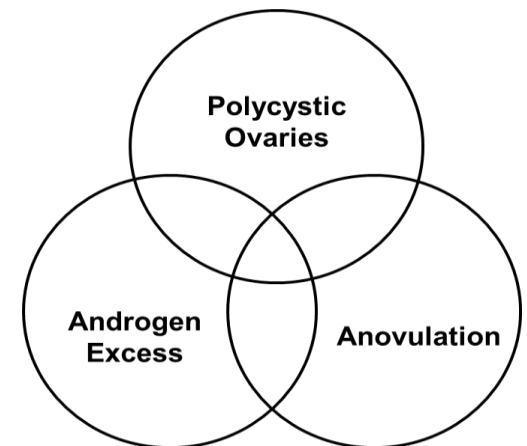
# Conclusion

# Recommendations (2018)

## Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome

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[9]Participants of the International PCOS Network are listed in the Appendix

# Conclusions

- CVD risk factors are clearly increased in PCOS mediated mostly by insulin resistance, obesity as well as hormonal processes.

- Overall clinical events remains unclear pending high quality studies.

- However, prevalence of CVD risk factors is increased, all women with PCOS should be regularly assessed for CVD risk factors  and global CVD risk.

# Conclusions

- Lifestyle intervention should be recommended in all those with PCOS and excess weight, central obesity and insulin resistance.
    - Not only metabolic points, but also it yields significant improvements in all symptoms of PCOS: anovulation and hyperandrogenism.
    - First line of treatment in overweight or obese women with PCOS.

# Thank you for your attentions