

# CARDIOVASCULAR EVENTS IN POLYCYSTIC OVARY SYNDROME

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# LONG TERM RISKS IN PCOS

- Young PCOS women present an increased risk of
  - type II diabetes
  - cardiovascular diseases
  - chronic liver disease
  - endometrial cancer

# INCREASED CV RISK IN YOUNG PCOS WOMEN

- A large number of studies has shown increased CV risk in young PCOS women
- Almost all CV risk factors including metabolic syndrome, atherogenic dyslipidemia, LDL levels, hypertension and C-reactive protein have been found elevated in young women with PCOS

# CV EVENTS IN PCOS

- It is still unclear whether CV events are increased in women with PCOS
- Contrasting data have been published and the quality of many studies is relatively low

# CV EVENTS IN PCOS WOMEN DURING REPRODUCTIVE AGE

- In a large Australian study (Hart et al JCEM 2015) hospitalization for cardiovascular diseases was increased in young PCOS women (mean age 35 years)
  - Ischemic heart disease 0.8% vs 0.2% in general population
  - Cerebrovascular ischemic disease 0.6% vs 0.2 in general population

Although this approach has many biases, it suggests a larger number of cardiovascular events in young population with PCOS

# CV EVENTS IN PCOS WOMEN DURING REPRODUCTIVE AGE

- An inherent difficulty is linked to the low number of CV events in young population
- In general population the prevalence of myocardial infarction at the age of 35 years is only 1.22 x 10,000 individuals
- A hospitalization based study may over-estimate the phenomenon
- Anyway, a 4 times increase may mean 5 cases of ischemic heart disease x 10,000 individuals

# RELATIVE RISK FOR CARDIOVASCULAR EVENTS IN NORMAL WOMEN DURING REPRODUCTIVE AGE

Number of events for 10,000 person-year	Myocardial infarction	Stroke
15-19 years	0.04	0.34
20-24 years	0.07	0.56
25-29 years	0.20	1.05
30-34 years	0.50	1.54
<b>35-39 years</b>	<b>1.22</b>	<b>2.33</b>
40-44 years	2.54	3.92
45-49 years	3.82	6.44

Modified from Lidegaard et al. NEJM 2012;366:2257-66

# NO INCREASED CV EVENTS IN FOLLOW-UP OF PCOS PATIENTS

- In our follow-up study, **no main CV events** were observed in PCOS women when they moved from their 20s to early 40s
- In several patients atherosclerotic plaques were present in their young age but resolved before the patients reached the menopausal age
- It suggests that the flexibility of CV system during young age may reduce the number of expected events

# AGING AND CV DISEASES

- In the normal population, occurrence of cardiovascular diseases is strictly related to age
- The number of main cardiovascular events is very low during young fertile age and starts increasing during late reproductive age
- The number of cardiovascular events strongly increases during 50s

# CARDIOVASCULAR EVENTS IN AGED PCOS

- One study that reviewed death certificates of 786 women in the United Kingdom who were diagnosed with PCOS at an average age of 26.4 years and followed for an average duration of 30 years **failed to show a statistically significant increase in cardiovascular mortality** (Pierpoint et al. J Clin Epidemiol 1998;51:581-6)
- However, this study has been criticized because the diagnosis of PCOS was based on historical data during a very large period (hospital records between 1930 and 1979) and was not supported by hormonal studies

# CARDIOVASCULAR EVENTS IN AGED PCOS

- In a successive report, the same authors (Wild et al Clin Endocrinol 2000;52:595-600) have studied a more restricted but more carefully selected cohort of patients (309 postmenopausal women who were diagnosed as affected by PCOS, before 1979, in United Kingdom).
- The authors did not observe any increase in coronary heart disease (odd ratio 1.5) but noted a higher prevalence of cerebrovascular accidents (odd ratio 2.8).

# CARDIOVASCULAR EVENTS IN AGED PCOS

- A more instructive study, because it included a large number of women and therefore had substantial statistical power, is the **Nurses Health Study (NHS)**, which followed 82,439 women for 14 years.
- The women with very irregular menses had a significantly increased relative risk of 1.5 (CI: 1.3-1.9) for coronary heart disease and 1.9 (CI: 1.3-2.7) for fatal myocardial infarction compared with eumenorrheic women.
- Since oligomenorrhea is an excellent surrogate marker for PCOS, these findings lend strong epidemiological support to the idea of increased cardiovascular risk in PCOS.

# CARDIOVASCULAR EVENTS IN AGED PCOS

- The findings of the NHS were corroborated by a sub study of the Women's Ischemia Evaluation Study (WISE) (Shaw et al JCEM 2008; 93:1276-84).
- 104 postmenopausal women with PCOS (defined as oligomenorrhea during the premenopausal years and elevated serum testosterone) were identified and followed prospectively for close to 10 years.
- **Multivessel cardiovascular disease was observed in 32% of PCOS women compared to 25% of non-PCOS women (odd ratio 1.7)** and it correlated with several factors, including persisting postmenopausal hyperandrogenism
- However, this study has been withdrawn because of a NIH evaluation found several mistakes in data collection

# LEICESTER STUDY

- A recent study has claimed important increase of cardiovascular events in aged PCOS women (Mani H et al. Clin Endocrinol 2013; 78:926-934)
- At the end of 20 years follow-up, the prevalence of MI in the age groups was:
  - 45–54 years: 1.9 %
  - 55–64 years: 6 %
  - >65 years: 27.3 %
- Odd ratios for the prevalence of MI compared to the local female population was 12.9 (CI: 3.4–48.6) in the group >65 years old

# LEICESTER STUDY

However:

- Only 11 patients had more than 65 years
- Only 83 patients had more than 55 years

# CV EVENTS IN AGED PCOS WOMEN

- In an other small (Schmidt et al. JCEM 2011; 96:3794-3803) study, 21 PCOS patients were followed until their 60s and **number of CV events was similar to that found in normal women of similar age**

# CV EVENTS IN AGED PCOS WOMEN

- Large and well planned follow up studies are needed to demonstrate increases of CV events in aged PCOS patients
- However, available data suggest that the number of CV events in aged PCOS patients is slightly increased but lower than that expected on the basis of risk calculation during young age

# CV EVENTS IN PCOS: SUMMARY

- A 3-4 times increase of cardiovascular events in young PCOS women is probable but still not demonstrated
- Anyway the number of events during young reproductive age is very low and also its increase of 3-4 times may not be sufficient to increase the total number of CV events in PCOS
- In aged PCOS the CV events are normal or slightly elevated

# DISCREPANCY BETWEEN CV RISKS AND EVENTS IN AGED PCOS

- The mechanisms of the discrepancy between CV risk and late events in PCOS are unclear
- Progressive normalization of CV risk during late reproductive age may have a main role
- Flexibility of CV system is much higher during reproductive age than in aged population

# CHANGES OF THE EXPRESSION OF PCOS DURING LATE REPRODUCTIVE AGE

- During late reproductive age, probably because of spontaneous reduction of ovarian and adrenal androgens, in a subgroup of patients the severity of PCOS reduces and in some patients the syndrome may disappear
- These spontaneous changes are very important for the future life of the patients with PCOS and our counseling should take in account the different possible evolutions of the disorder

# CHANGES OF THE EXPRESSION OF PCOS DURING LATE REPRODUCTIVE AGE

- Moving from 20-25 to 40-45 years age, in PCOS the following changes occur:
  - Androgen secretion reduces by 20-30%
  - Ovulation appears in about 50% of PCOS patients
  - A number of these women will have spontaneous pregnancies and children
- These changes influence not only the reproductive life but also the metabolic and CV risk of PCOS patients

# IMPROVEMENT OF PCOS DURING LATE REPRODUCTIVE AGE REDUCES CARDIOVASCULAR RISK

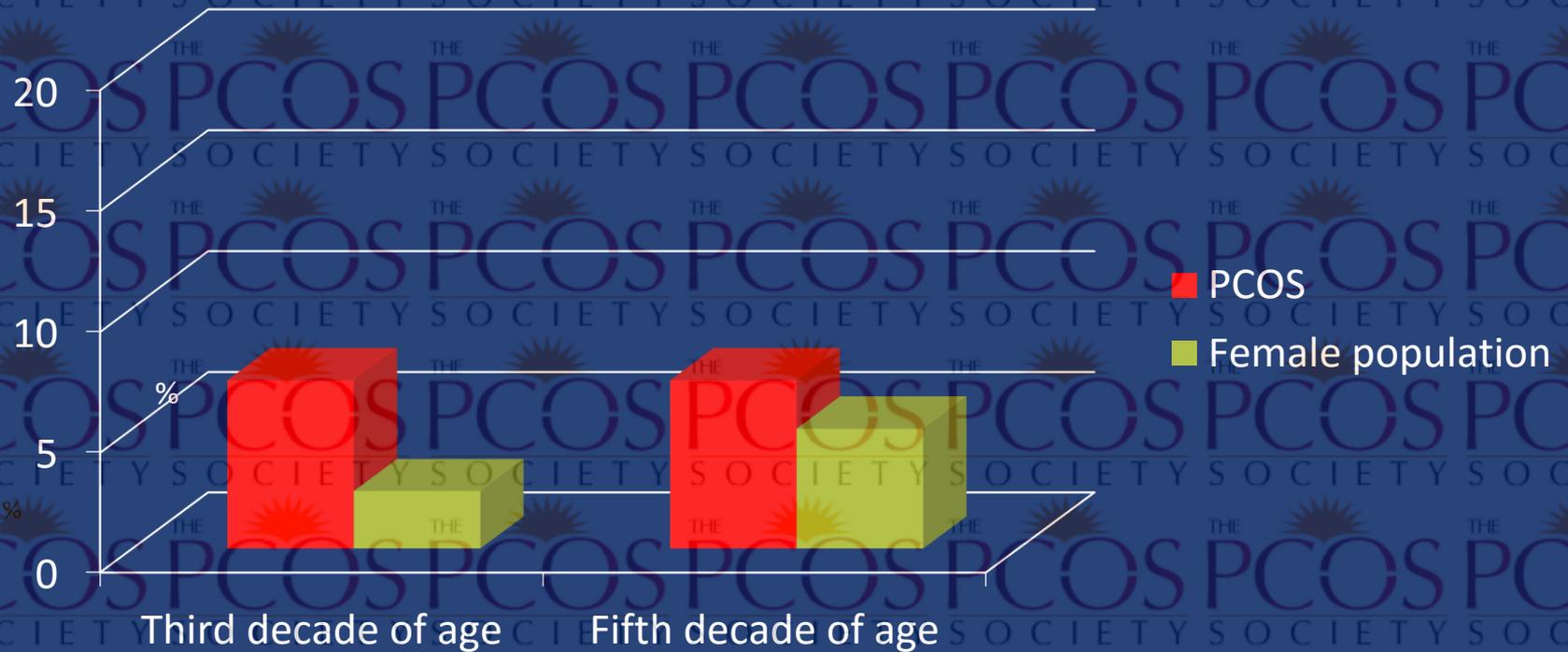
EMERGENCE OF OVULATORY CYCLES WITH AGING IN WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) ALTERS THE TRAJECTORY OF CARDIOVASCULAR AND METABOLIC RISK FACTORS

Carmina E, Campagna AM, Lobo RA

*Hum Reprod* 2013, 28:2245-52

○ **Conclusions: Prevalence of metabolic syndrome and dyslipidemia tend to normalize with aging. It is mainly depending on improvement of lipid parameters in women who attain ovulatory cycles.**

# PREVALENCE OF METABOLIC SYNDROME IN PCOS WOMEN OF DIFFERENT REPRODUCTIVE AGE



# LDL VALUES IN 2 GROUPS OF PCOS PATIENTS WHO WERE FOLLOWED FOR 20 YEARS

## LDL-cholesterol at a mean age of 42 years



# APPEARANCE OF OVULATORY CYCLES DURING LATE REPRODUCTIVE AGE ATTENUATES CV RISK IN PCOS

- The occurrence of ovulatory function during late reproductive age in women with PCOS is associated with an attenuation of cardiovascular risk.
- A negative correlation was observed between the appearance of ovulatory cycles and the increase in LDL-cholesterol.
- In patients who remained anovulatory, total, LDL-cholesterol and non-HDL-cholesterol values significantly increased and prevalence of metabolic syndrome and CV risk remained significantly higher than in general population.

# IMPROVEMENT OF CARDIOVASCULAR RISK DURING REPRODUCTIVE AGE IN YOUNG PCOS WOMEN

- Other studies (Tehrani et al. Plos One 2015, Sep 11, Epub) have suggested that the cardiovascular risk tends to normalize with age in PCOS
- Young PCOS women followed for a mean period of 6 years presented tendency to normalize their risk linked to altered lipid profile and insulin resistance

# AGING ATTENUATES CV RISK IN PCOS

- All these factors determine a generalized reduction of cardiovascular risk in PCOS women when they approach menopause.
- However, the population of PCOS women remain heterogeneous with some women presenting normalization of cardiovascular risk and others remaining with a substantial risk

# DIVERGENT EVOLUTION OF TWO SUBGROUPS OF PCOS DURING LATE REPRODUCTIVE AGE

- There is a divergent evolution of two groups of women with PCOS during their late reproductive age
- One subgroup improves its reproductive function and reduces the cardiovascular risk
- Another subgroup continues to have altered reproductive function and high metabolic and cardiovascular risk

# INCREASE OF CV RISK FACTORS IN PCOS DURING LATE REPRODUCTIVE AGE

	Total Cholesterol	NON-HDL C	LDL-C	Metabolic Syndrome
Patients who remain anovulatory	++	++	++	+
Patients who become ovulatory	+	NO	NO	NO

# LONG TERM MANAGEMENT OF PCOS WOMEN

- The emerging data on changes in metabolic and cardiovascular risk with age in PCOS have complicated our approach to long term management of young PCOS women.
- What should we do?
  - Treat all young women with PCOS who present a risk?
  - Wait until the age of 40s to concentrate the treatment in women who do not normalize or substantially improve their risk?

# LONG TERM MANAGEMENT OF PCOS WOMEN

- No clear answer exists to these questions and many more and more prolonged follow up studies are needed. However, a rational approach may be that to limit the treatment only to young patients presenting more severe metabolic involvement.
- In fact, data on prevalence of type II diabetes with age seem to indicate a high risk of conversion from altered glucose tolerance to overt diabetes in reproductive age patients.
- Therefore, altered glucose tolerance should always be actively treated also during young age.

# LONG TERM MANAGEMENT OF PCOS WOMEN

- Patients who do not present altered glucose tolerance but present increased cardiovascular risk may probably wait until the age of 40s.
- At that time, a careful analysis of CV risk should be performed and all patients with increased CV risk should be actively treated.