Reproductive Health in Non Alcoolic Fatty Liver Disease (NAFLD)

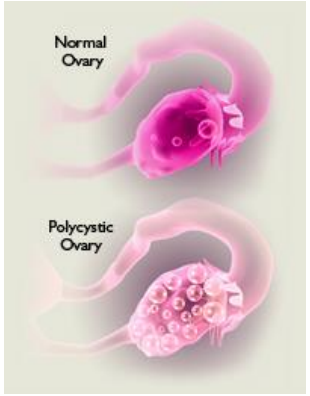
Pr Sophie Christin-Maitre
Reproductive Endocrine Unit, Hôpital Saint-Antoine, AP-HP
Université Pierre et Marie Curie
INSERM U933
Paris, France

?

NAFLD

Polycystic ovary syndrome

?



?

NAFLD

Male hypogonadism

?

Definition of polycystic ovary syndrome (PCOS)

- 2003 : Rotterdam consensus

At least 2 of the 3 following criteria :

1) Oligomenorrhea or anovulation

2) Clinical and/or biological signs of hyperandrogenia

3) Polycystic ovaries on ultrasound

excluding tumoral hyperandrogenism,

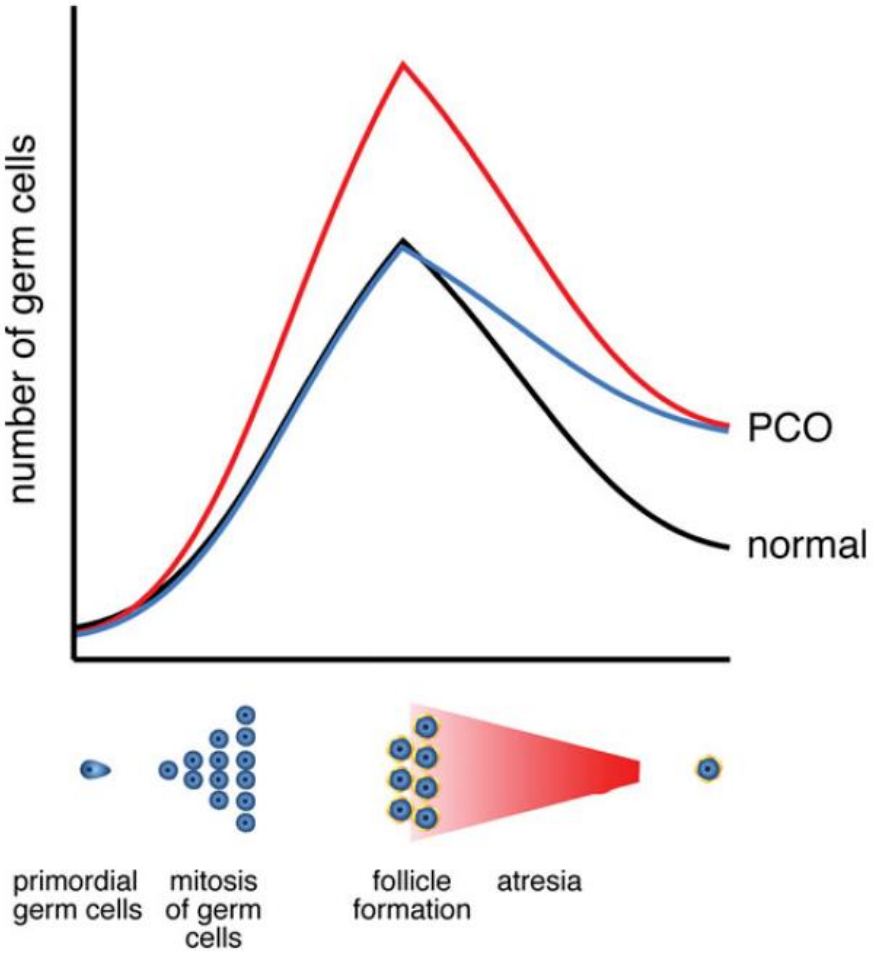
21 hydroxylase deficiency and Cushing syndrome

Fertil Steril 81: 19-25, 2004; Hum Reprod 2004

Definitions of PCOS

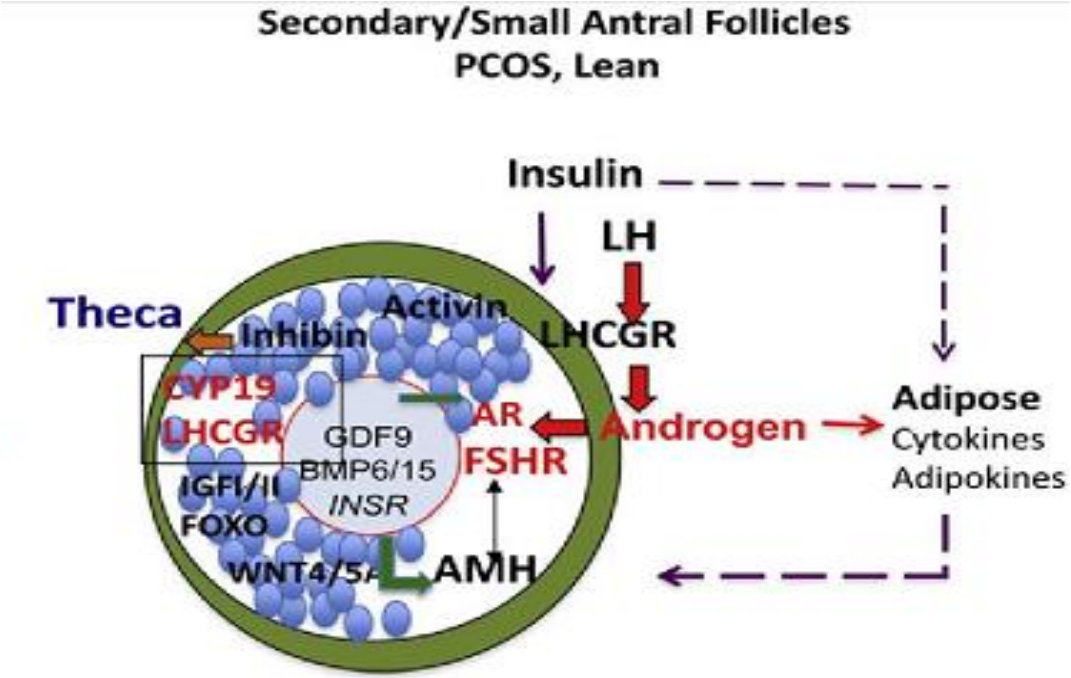
NIH/NICHD (must meet both criteria)	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation • Polycystic ovaries	• Ovarian dysfunction and/or polycystic ovaries

PCOS : accumulation of small follicles

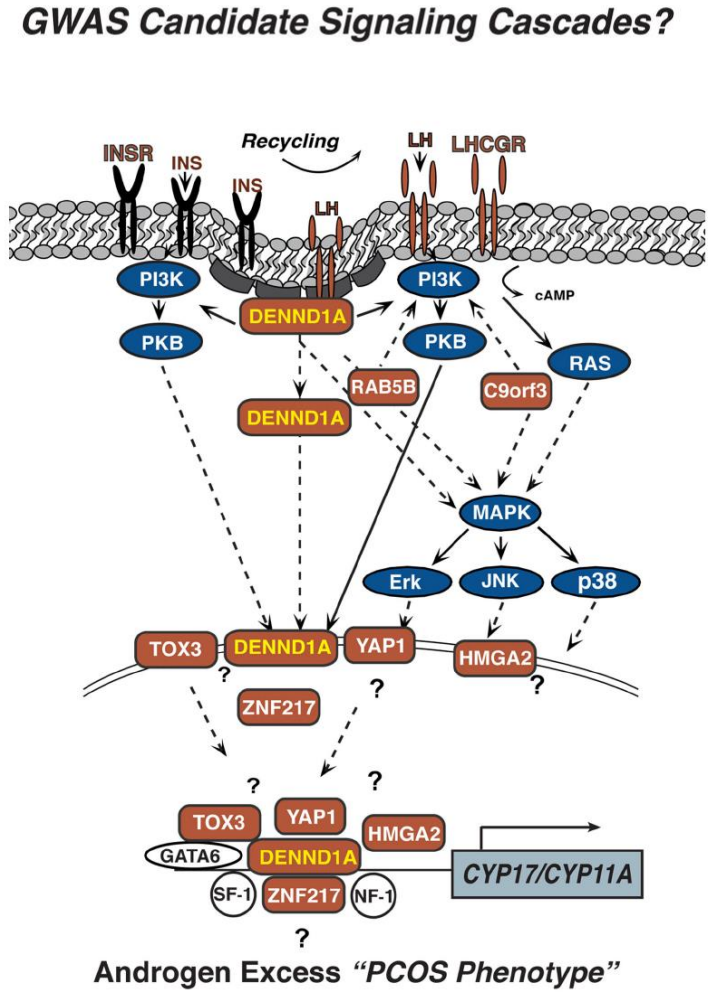


Human Reproduction Update, Vol.14, No.4 pp. 367–378, 2008

PCOS : abnormal folliculogenesis

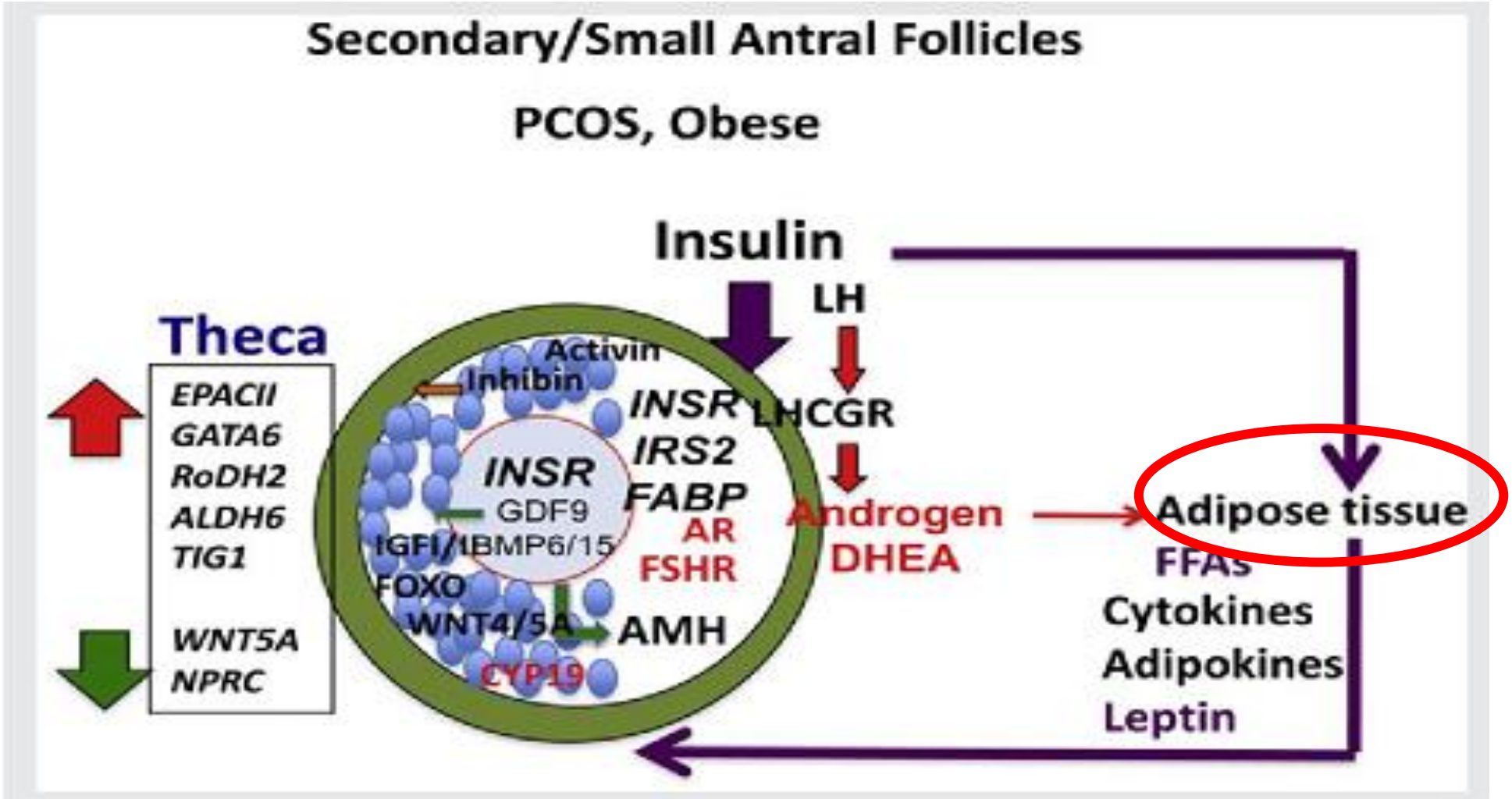


Dumesic. Ontogeny of the ovary in PCOS. Fertil Steril 2013.



Trends in Endocrinology 2016

PCOS : Abnormal folliculogenesis



Dumesic. Ontogeny of the ovary in PCOS. Fertil Steril 2013.

Polycystic ovary syndrome

- Prevalence of PCOS : 8-18 % of female population
  more than 25% in obese women

March WA et al. Hum Reprod 2010; 25: 544

- First cause of female infertility

- Increased risk of metabolic syndrome
- Increased risk of type 2 diabetes
- Increased risk of dyslipidemia
- Increased risk of cardiovascular diseases

Legro R et al. JCEM 2013; 98: 4565-92; Welt C et al. JCEM 2013; 98 : 4629-38

First description of NAFLD in a PCOS woman

Endocrine Pratice 2005

- POLYCYSTIC OVARY SYNDROME AND SEVERE NONALCOHOLIC STEATOHEPATITIS: BENEFICIAL EFFECT OF MODEST WEIGHT LOSS AND EXERCISE ON LIVER BIOPSY FINDINGS

  Ann J. Brown, David A. Tendler, Robert G. McMurray, Tracy L. Setji

- Case Report

A 24 year old woman referred for long term high serum aminotransferase levels, irregular menses, hirsutism

Liver biopsy : severe non alcohoolic steatohepatitis

11.5 % weight loss in 8 month

Liver biopsy at 13 months : decrease in steatosis, reduction in inflammation

- Prevalence of PCOS among women with NAFLD

71% in one small study n= 14

Brzozowska MM et al. J *Gastroenterol Hepatol 2009; 24: 243-247*

Increased risk of NAFLD in women with PCOS

Table 2. Frequencies of Hepatic Steatosis in Control Women, Patients With PCOS, and Men and in Nonobese vs Obese Subjects

Hepatic Steatosis	Control Women (n = 25)	PCOS (n = 55)	Men (n = 26)
Grade			
0	18 (72)	34 (62)	15 (58)
1	6 (24)	8 (15)	6 (23)
2	1 (4)	10 (18)	3 (11)
3	0 (0)	3 (5)	2 (8)

Data are counts (percentages). To fulfill the χ^2 assumption that no more than 20% of the expected counts were less than 5 and all individual expected counts were 1 or greater, we compared the grade 0 category with the category that resulted from merging the grades 1, 2, and 3 categories. After merging, no cells had expected count less than 5, and the minimum expected count was 9.2 for the comparison among groups and 14.7 for the comparison between nonobese and obese subjects. No difference in the frequency of hepatic steatosis was observed between groups ($\chi^2 = 1.217$, $P = .544$), yet hepatic steatosis was much more frequent in obese subjects compared with nonobese individuals ($\chi^2 = 51.572$, $P < .001$).

Borruel S et al. J Clin Endocrinol Metab, March 2013, 98(3):1254–1263

World Journal of Gastroenterology

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Review of nonalcoholic fatty liver disease in women with polycystic ovary syndrome

Carly E Kelley, Ann J Brown, Anna Mae Diehl, Tracy L Setji

NAFLD in 15 to 55% of women with PCOS

Population tested ? PCOS definition ? NAFLD diagnosis ?

October 21, 2014 | Volume 20 | Issue 39 |

The most recent study :

Human Reproduction, Vol.31, No.6 pp. 1347–1353, 2016
Advanced Access publication on April 12, 2016 doi:10.1093/humrep/dew076

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

Non-alcoholic fatty liver disease is associated with insulin resistance and lipid accumulation product in women with polycystic ovary syndrome

D. Macut[1,*], K. Tziomalos[2], I. Božić-Antić[1], J. Bjekić-Macut[3], I. Katsikis[4], E. Papadakis[4], Z. Andrić[3], and D. Panidis[4]

600 PCOS women

125 control women

NAFLD and PCOS

- Rotterdam criteria
- NAFLD liver fat score :

$[-2.89 + 1.18 \times$ metabolic syndrome (MetS) (yes $= 1$/no $= 0) + 0.45 \times$ T2DM (yes $= 2$/no $= 0) + 0.15 \times$ fasting serum insulin (mU/l) $+ 0.04 \times$ AST (U/l) $- 0.94 \times$ AST/ALT] and a value of > -0.640 was considered diagnostic of NAFLD

Kotronen et al. 2009

- Free androgen index : FAI = (testosterone X 100)/ SHBG
  if FAI > 8 definition of hyperandrogenia

Mathur et al. 1981

- Homesostasis Model Assesment

  HOMA-IR score = insulin (mIU/L) x glucose (mmol/L) / 22.5

Mattews et al. 1985

- Lipid accumulation product (LAP) = [(Waist circumference -58) x TGs]

- Prevalence of NAFLD in PCOS

50.6% versus 34.0% in controls, matched for BMI

(p = 0.002)

=> What are the factors associated with NAFLD?

Human Reproduction, Vol.31, No.6 pp. 1347–1353, 2016

Factors associated with NAFLD in PCOS women

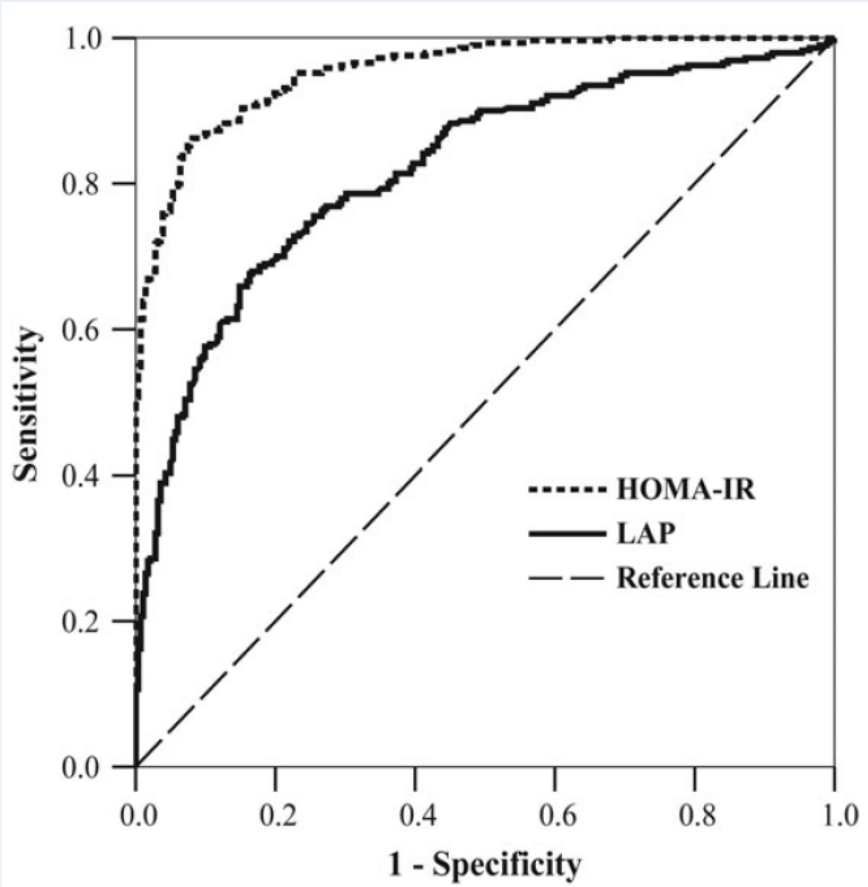


Figure 1 ROC curve: HOMA-IR and lipid accumulation product (LAP) as predictors of the NAFLD liver fat score of > -0.640.

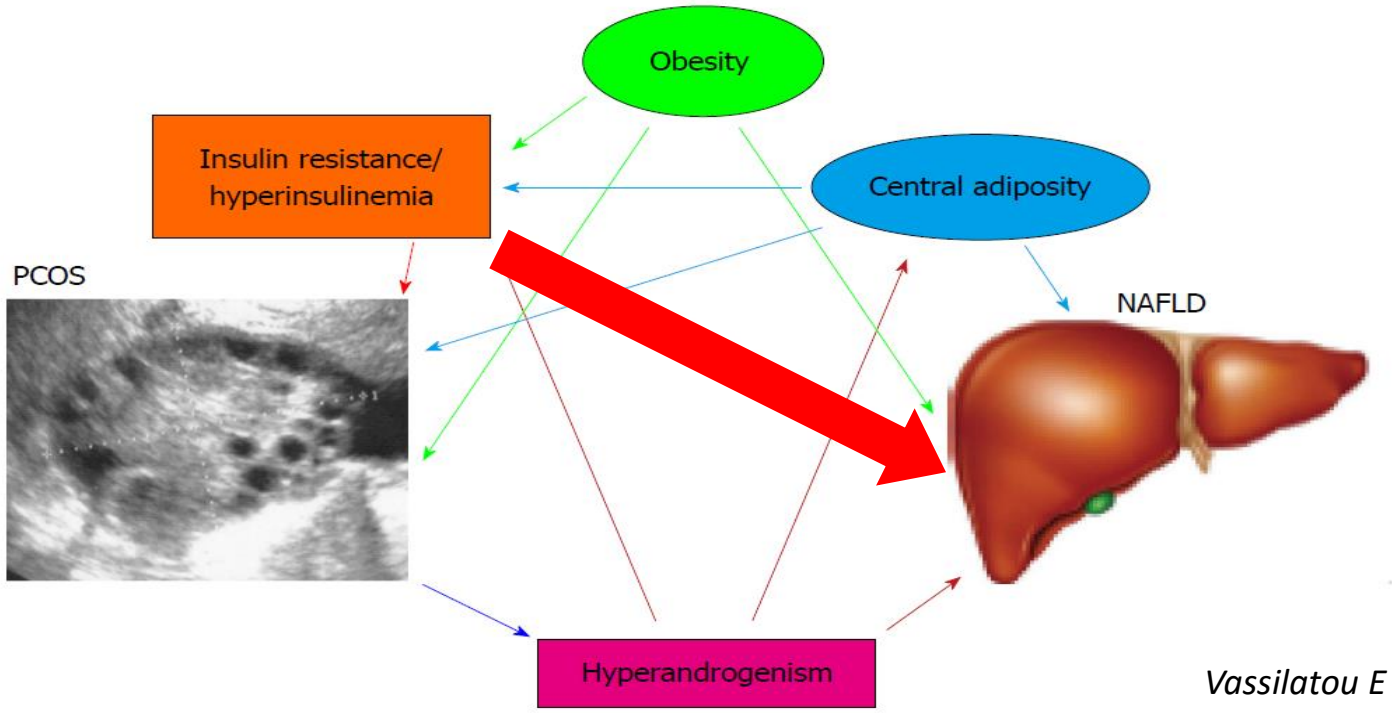
Human Reproduction, Vol.31, No.6 pp. 1347–1353, 2016

Potential conclusions concerning NAFLD and PCOS

- Insulin Resistance is associated with the occurrence of NAFLD +++

=> Life style intervention and weight loss are potentially beneficial on NAFLD

=> Tt with metformin ?

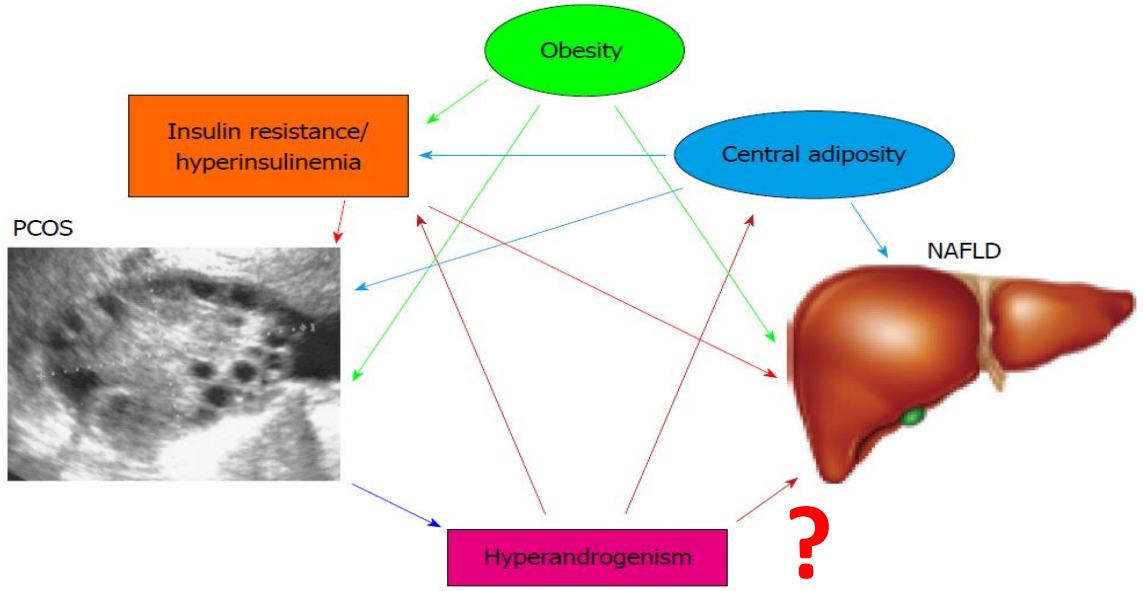


Vassilatou E *World J Gastroenterol* 2014 July 14; 20(26): 8351-8363

Potential conclusions concerning NAFLD and PCOS

- LAP could represent an unexpensive marker of NAFLD ?

- The direct role of serum androgen levels on NAFLD remains controversial



BUT in this study…

- Androgens are not measured by LC- MS
- No magnetic resonance spectroscopy, no liver biopsies performed
- No answer about the potential mechanisms involved in the pathogenesis of NAFLD in PCOS women

Protective role of estrogen ?

Human Reproduction, Vol.31, No.6 pp. 1347–1353, 2016

Protective role of estrogen on NAFLD ?

- In postmenopausal women with low E2, higher prevalence of NAFLD

  Study of Health in Pomerania, Northeast Germany

  Volzke H et al. Gut 2007; 56: 594-5

- Current oral contraceptive pills users have a 50% lower odds of NAFLD than never users

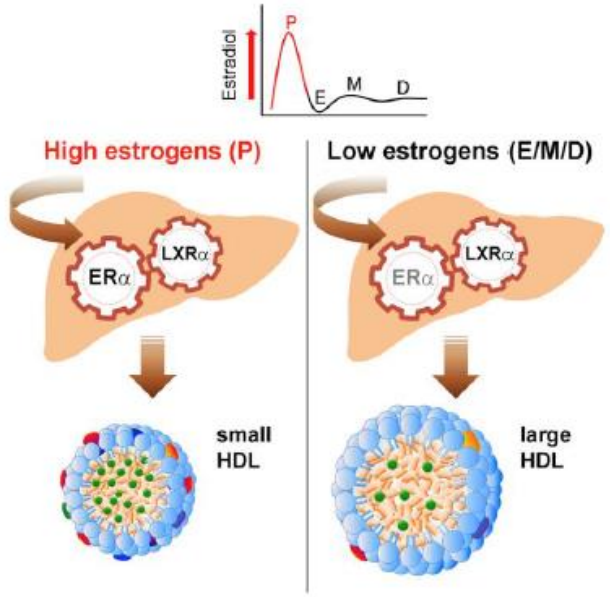
  Liu SH et al. J Gastroentrol 2013; 48: 1151-1159

Protective role of estrogen on NAFLD ?

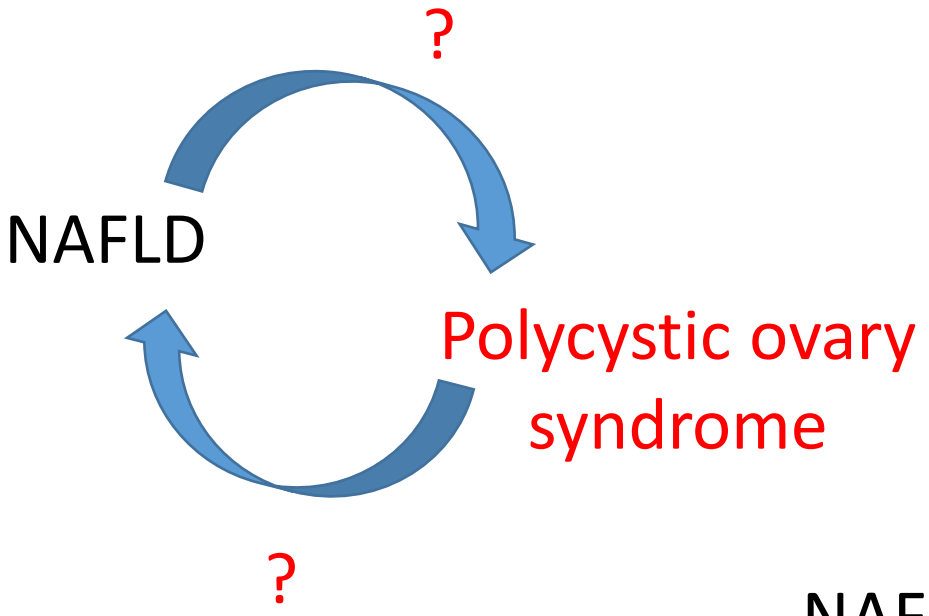
- Animal models

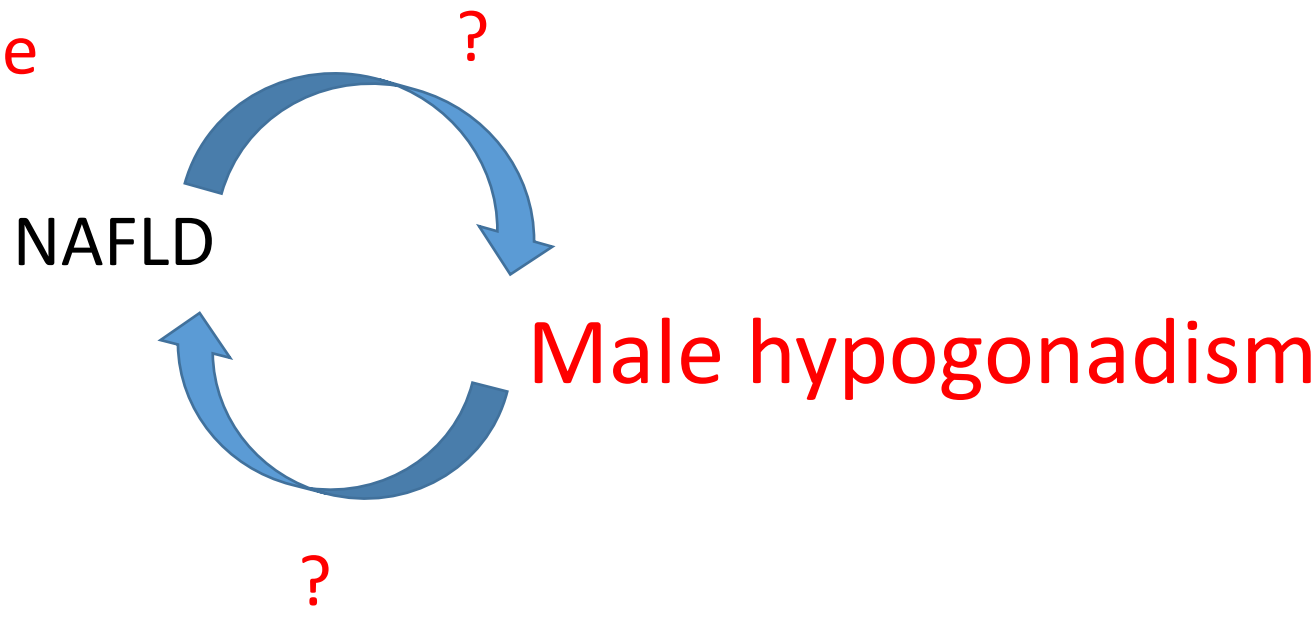
EX : - Erα knock-out mice : increased fat in the liver

- Selective ablation of Erα in the liver => deposition of fat in the liver



Della Torre S et al. Cell report 2016 ; 15 : 360-71


?
NAFLD
Polycystic ovary syndrome
?


?
NAFLD
Male hypogonadism
?

NAFLD in males

- Lower testosterone levels are associated with accumulation of abdominal and visceral fat

  217 men from HERITAGE Family study

  Couillard C et al. JCEM 2000

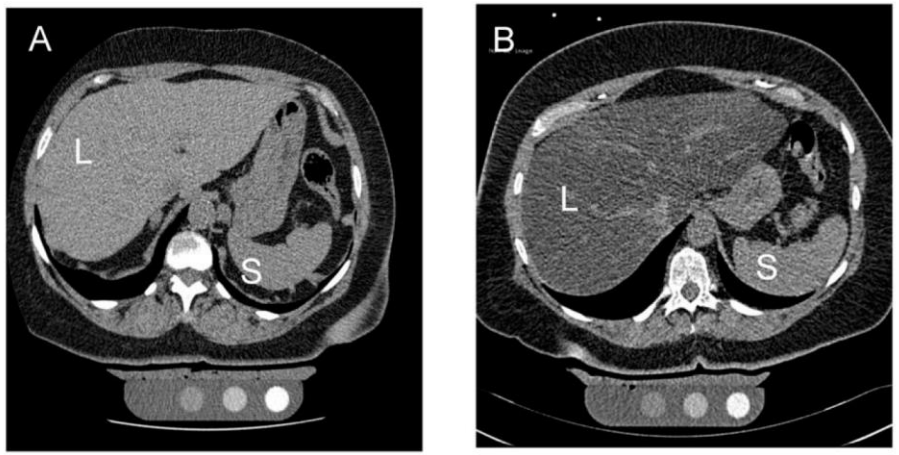
- In a retrospective study including 1912 men, hepatic steatosis is correlated with low testosterone levels (< 14.2 nmol/L)

  Volzke H et al. Int J Androl 2010

NAFLD in males

- In Multiethnic Study of Atherosclerosis study (USA)

  n= 3213 men aged 45-84 years



=> Lower levels of SHBG and higher levels of E2

in men are associated with NAFLD

Lazo et al *Clin Gastroenterol Hepatol*. 2015 September ;

Nonalcoholic fatty liver disease and alteration in semen quality and reproductive hormones

Yan Li[a], Lei Liu[b], Bin Wang[a], Dongfeng Chen[a] and Jun Wang[b]

Table 1. Baseline characteristics of the study cohorts

Parameter	Controls ($N=94$)	NAFLD ($N=102$)	P
Age (years)	34.5±5.6	35.4±4.7	0.68
BMI (kg/m^2)	22.4±2.5	23.6±3.2	0.08
Abstinence duration (days)	5.3±1.7	5.4±1.6	0.72
Coital frequency/month	10.0±2	10.0±3	1.68
Smoking (%)	23 (24.5)	27 (26.4)	0.12
Alcohol consumption (%)	31 (33.0)	35 (34.5)	0.72
AST (U/l)	24.8±7.5	59.3±18.1	0.03
ALT (IU/l)	23.4±12.6	65.3±37.8	0.01
Triglycerides (mmol/l)	1.2±0.6	3.9±2.3	0.02
HDL-c (mmol/l)	1.4±0.6	1.7±0.8	0.04
GLU (mmol/l)	4.9±1.0	5.7±1.6	0.32

Data are expressed as mean±SD or frequency (percentage).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLU, glucose; HDL-c, high-density lipoprotein-cholesterol; NAFLD, nonalcoholic fatty liver disease.

Original article

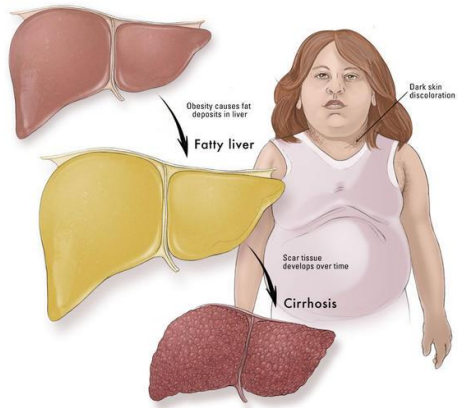
Nonalcoholic fatty liver disease and alteration in semen quality and reproductive hormones

Yan Li[a], Lei Liu[b], Bin Wang[a], Dongfeng Chen[a] and Jun Wang[b]

Serum T and SHBG lower in men with NAFLD

Sperm concentration (p=0.04), sperm count (p=0.01) and total mobility (p=0.03) were lower in men with NAFLD compared to normal men

CONCLUSIONS



- In postmenopausal women
  and in PCOS women,
  NAFLD is more prevalent than in control women

- Liver evaluation in PCOS women is useful especially in obese women +++ , *although a systematic evaluation has not been recommended by Endocrine Society clinical practice guidelines in 2013*

- Mode of evaluation : aminotransferase level and ultrasound? Frequency of evaluation?

CONCLUSIONS

- In men,

Low testosterone serum level and low SHBG are correlated with NAFLD prevalence

Potential impact of NAFLD on sperm count and mobility

What is the potential impact of androgen tt on NAFLD ?


ngiyabonga
danke
謝謝
teşekkür ederim
спасибо
dank je
thank you
gracias
tapadh leat
bedankt
hvala
mauruuru
mochchakkeram
dziękuję
go raibh maith agat
sukriya
kop khun krap
sagolun
arigatō
takk
dakujem
obrigado
grazie
terima kasih
мерси
감사합니다
ευχαριστώ
merci