

PCOS: The rationale for metformin treatment



Laure Morin-Papunen, MD, PhD
Dept. of Obstetrics and Gynecology
University Hospital of Oulu, Oulu, Finland

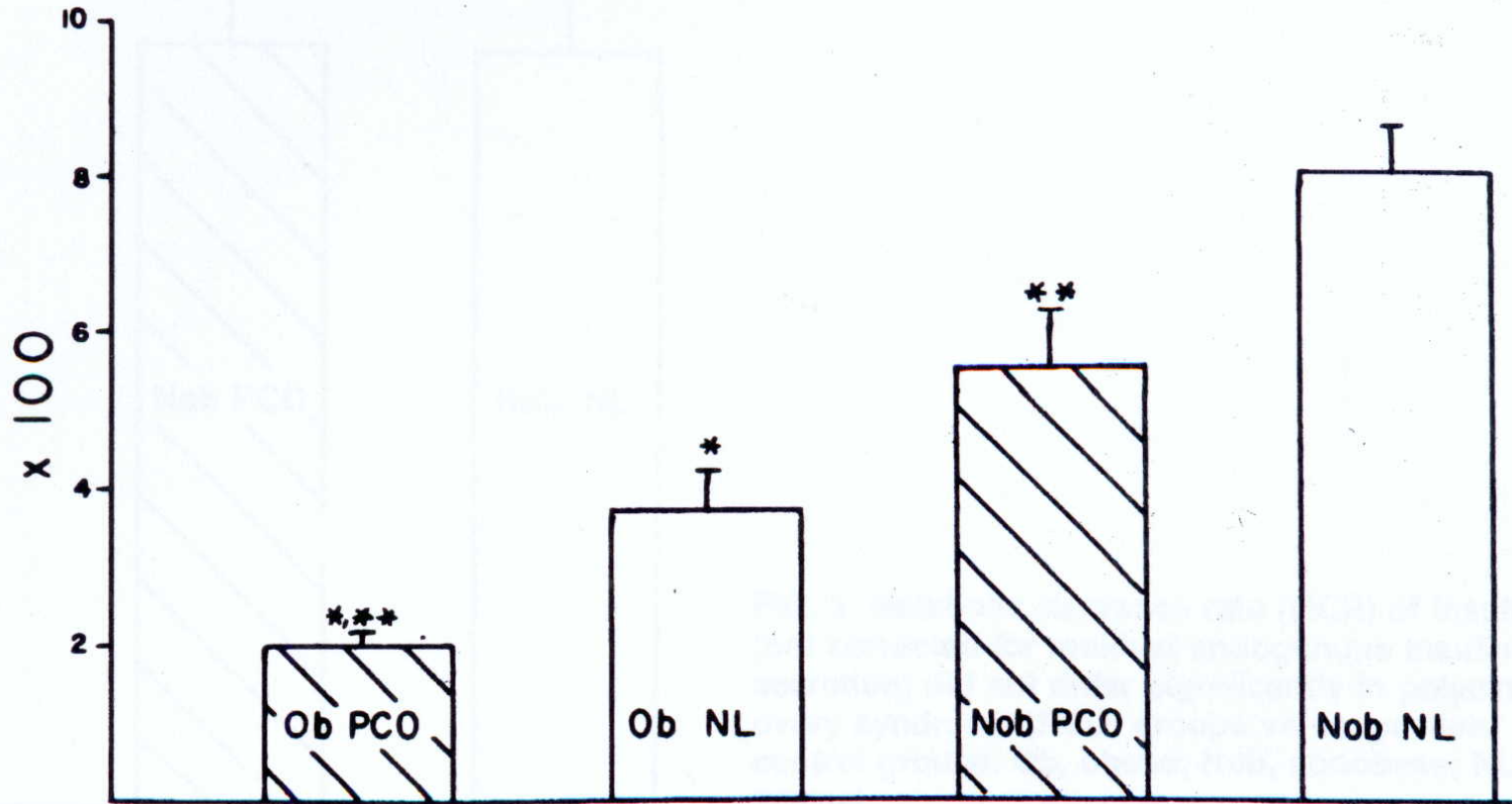
The rationale for metformin in PCOS

- Mechanisms of action
- Treatment of anovulation
- Treatment of the metabolic disorders

Metformin in PCOS

Mechanism of action

Insulin sensitivity in PCOS

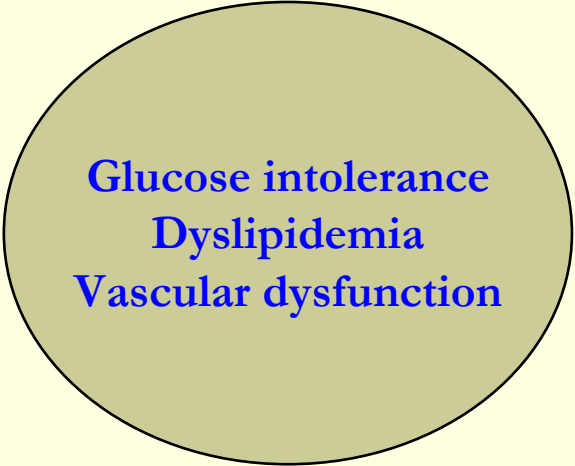
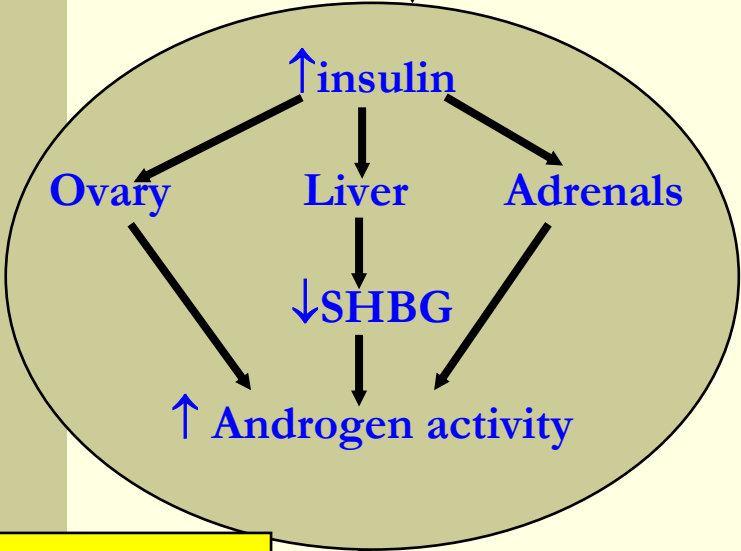


(Dunaif 1987)

**Insulin resistance
Obesity**

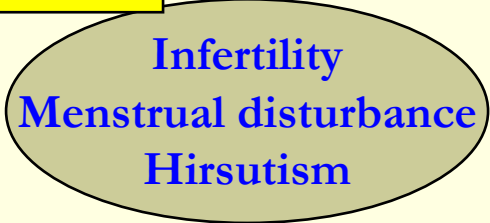
**Endocrine
manifestations**

**Metabolic
manifestations**



**Clinical
presentation**

**Long-term
sequelae**



after Harborne et al 2003

Metformin: mechanism of action

- Still unclear
- Antihyperglycemic drug, not a "true" insulin sensitizer

METFORMIN

LIVER

↑ **AMPK activity in hepatocytes**
⇒ ↑ **insulin sensitivity**
⇒ gluconeogenesis ↓
+ **hepatic glucose output** ↓

MUSCLE FAT

↓ FFAs
⇒ ↑ glucose transport
⇒ ↑ insulin sensitivity

INTESTINE

⋮ intestinal absorption of glucose
↓

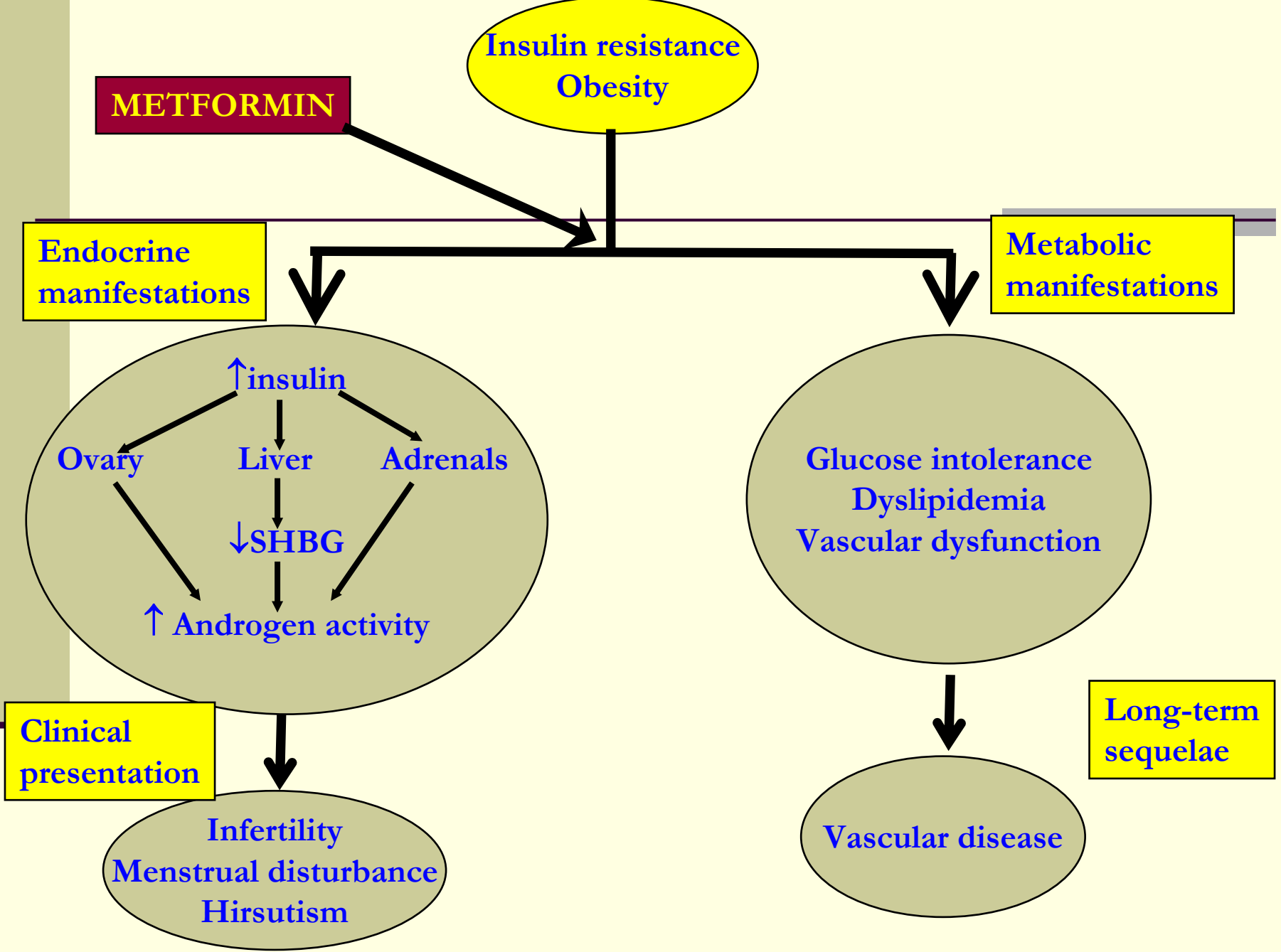
PANCREAS

no direct effect on insulin secretion
⇒ **SAFE!**

OVARY

? ⋮ androgen secretion
↓

*(Zhou 2001,
Natali and Ferrannini 2006)*



after Harborne et al 2003

Beneficial effect on metabolic and clinical parameters

- ↓ insulin (about 20-30%) and testosterone (about 20%)
- ↑ SHBG
- Hirsutism: minimal/modest effect
- Acne: beneficial effect in one non-controlled study (*Kolodziejczyk 2000*)
- Menstrual regularity: restored in 25 to 70% of cases (*Lord 2003, Kashyap 2004*)

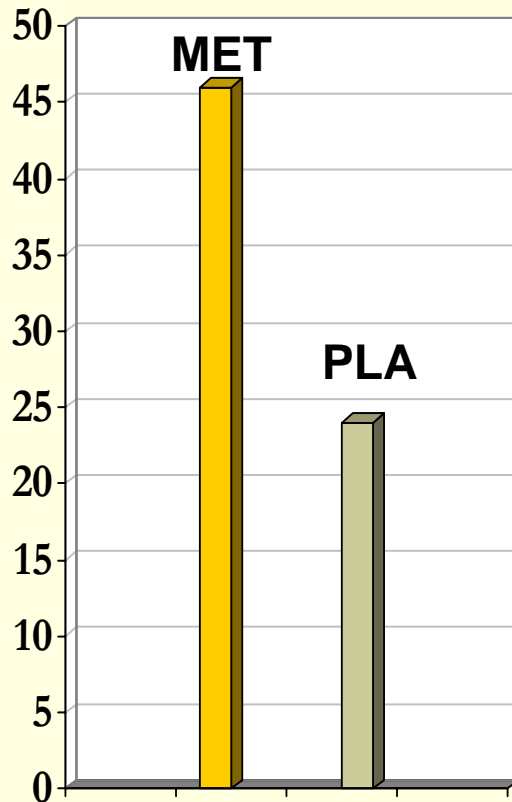


Metformin in PCOS



Treatment of anovulation

Metformin better than placebo



■ Restoration of ovulation

■ OR for metformin

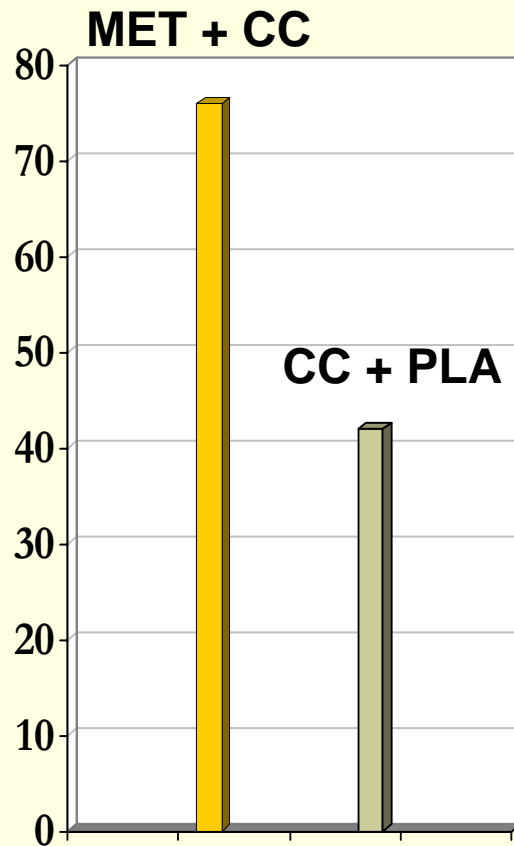
1.5-3.9 (2.2-6.7)

■ Pregnancy rate

■ OR **1.07 (0.5 – 1.1)**

(Lord 2003, Kashyap 2004)

Metformin improves sensitivity to CC (CC-sensitivity not defined)



■ Restoration of ovulation
■ **OR for metformin**
3.0 - 4,4 (CI 1.7-8.2)

■ Pregnancy rate
■ **OR for metformin**
3.6 - 4,4 (CI 1.1-9.9)

(Lord 2003, Kashyap 2004)

No benefit from the combination of metformin to CC (*Moll et al 2006*)

	CC + MET (n= 111)	CC + PLA (n= 114)	P-value
BMI	28.5 kg/m ²	27.8kg/m ²	
ovulation rates	64%	72%	NS
ongoing pregnancy rate	40%	46%	NS
miscarriage rate	12%	11%	NS
discontinuation (side-effects)	16%	5%	5-16%

CC better than metformin, no benefit from the combination (*Legro et al., NEJM 2007*)

	CC + PLA (N=209)	MET + PLA (N=208)	Combination (N=209)
BMI	36.0 kg/m ²	35.6 kg/m ²	34.2 kg/m ²
ovulation	49%	29%	60.4%
conception	29.7%	12%	38.3%
pregnancy	23.9%	8.7%	31.1%
live birth	22.5%	7.2%	26.8%
pregnancy loss	8.3%	20.8%	9.2%

Why these discrepancies?

- effect of obesity?
 - metformin ineffective if massive obesity ($\text{BMI} \geq 35 \text{ kg/m}^2$)
 - first weight loss, then metformin when $\text{BMI} < 35 \text{ kg/m}^2$? (*Balen et al 2006*)
 - but no differences in BMI subgroups analyses (*Legro et al. 2007*)
- extended-release form less effective than immediate-release form?

Why these discrepancies?

- High level of side-effects (diarrhea) in the metformin group compared with the CC group
⇒ better compliance in the CC group?
- Does it exist a subgroup of responders?
 - how to define predictive factors for a response to metformin?

Metformin improves sensitivity to CC (CC – resistant women)?

- 4 RCTs and 2 prospective studies (*Siebert 2006*)
 - restoration of ovulation
OR for metformin **6.8** (CI 3.6 – 12.9)
- Pregnancy rates
 - OR for metformin **1.7** (CI 1.2- 2.3)
- Live birth rates
 - metformin + CC better than CC alone
OR **6.4** (CI **1.2 – 35**) (*Moll 2007*)

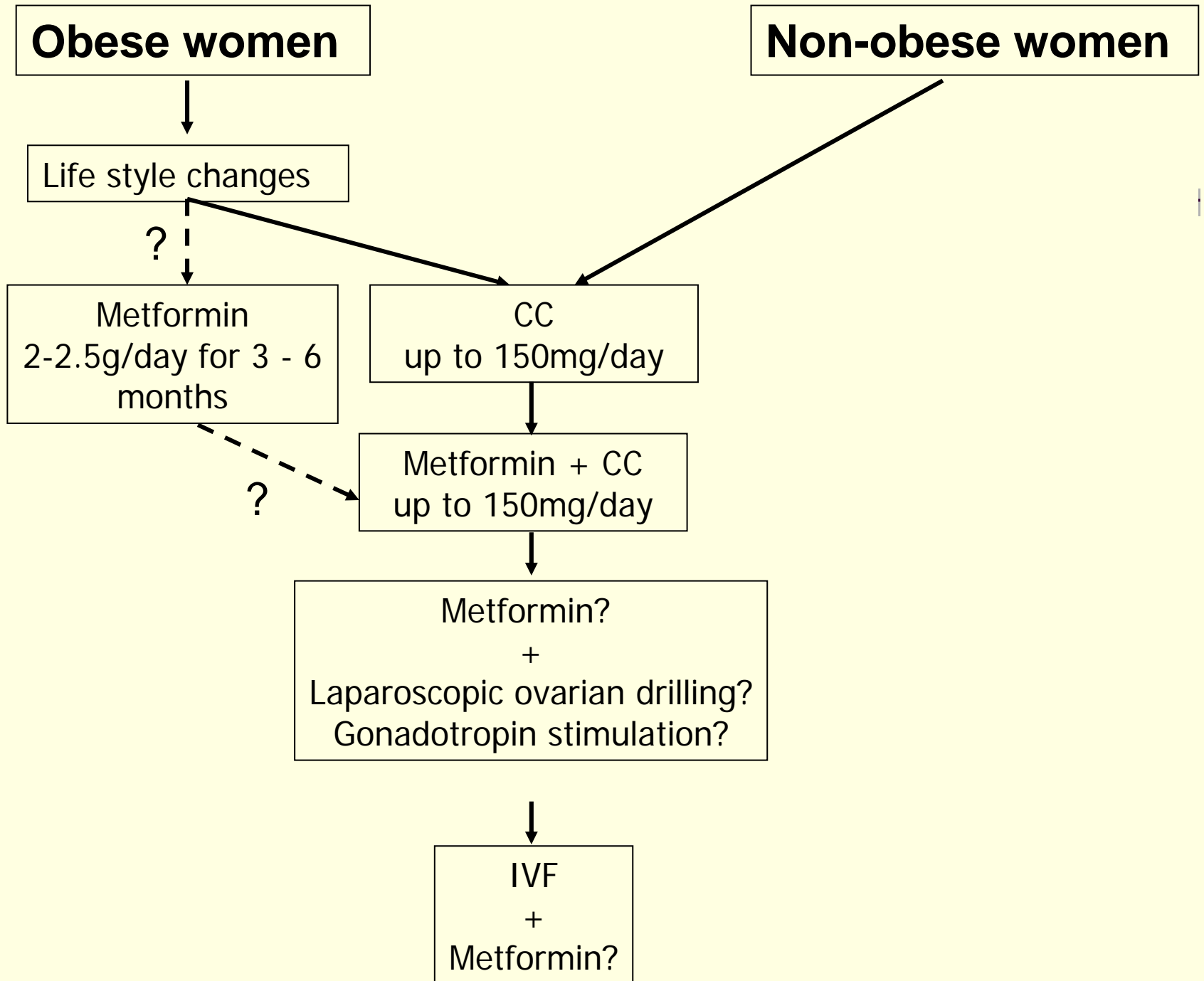
Metformin improves sensitivity to gonadotropins?

- Meta-analysis (*Costello 2006*)
 - 3 RCTs
 - No improvement of rates of ovulation or pregnancy
 - Small number of trials
 - Small sample sizes

(De Leo et al 1999, Yarali et al 2002, Tasdemir et al 2004)

Metformin improves IVF stimulation?

- Two meta-analyses (*Costello 2006, Moll 2007*)
- No improvement
 - pregnancy rates
 - live birth rates
- ↓ risk of OHSS (**OR=0.21- 0.33**, CI:0.11-0.80)



Metformin reduces miscarriage rate?

- Two retrospective studies
 - ↓ from **45-73 %** to **9-10 %** (*Glueck 2001, Jakubowicz 2002*)
- One prospective study
 - no effect (*Heard 2002*)
- Four RCTs
 - beneficial effects: metformin vs. placebo: ↓ **x 2-4** miscarriage rate (*Palomba 2004, 2005*)
 - no beneficial effect (*Moll 2006, Legro 2007*)

Metformin reduces risk of GDM?

- Controversial results
 - metformin throughout pregnancy
 - GDM incidence ↓ from 30% to 12%
(Glueck 2002, 2004, 2007)
 - no significant effect, but less complications of pregnancy in the metformin group
(Vanky 2004)

Metformin in pregnancy

■ Safety?

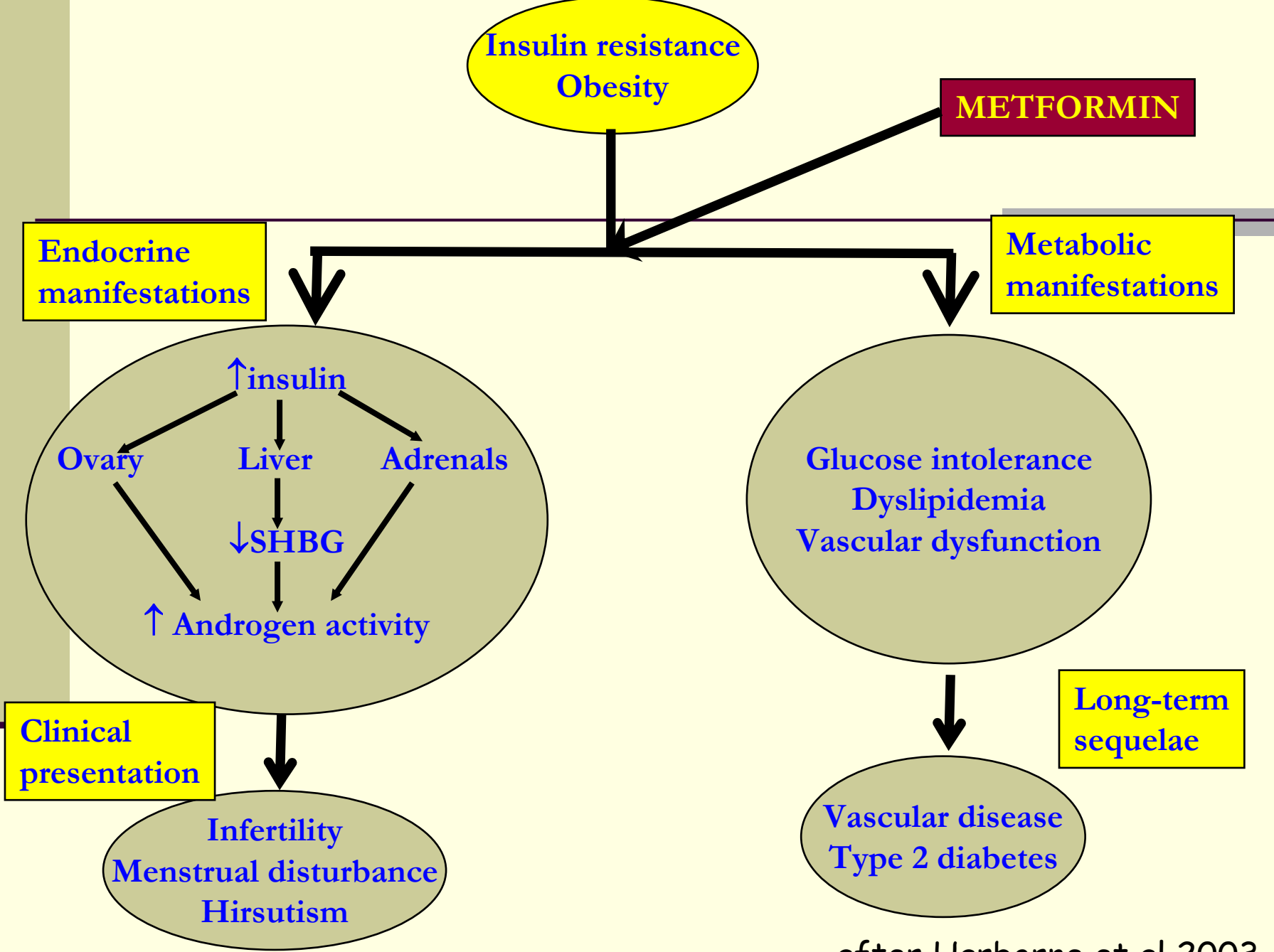
- No risk for the fetus (*Glueck 2004*)
- Passes the placenta \Rightarrow long-term effects on the fetus? (*Vanky 2005*)
- Should be stopped at the positive pregnancy test (*Norman 2005*)

■ Indications?

- Recurrent miscarriage?
- GDM in a previous pregnancy?
- Abnormal OGTT/GDM in ongoing pregnancy?

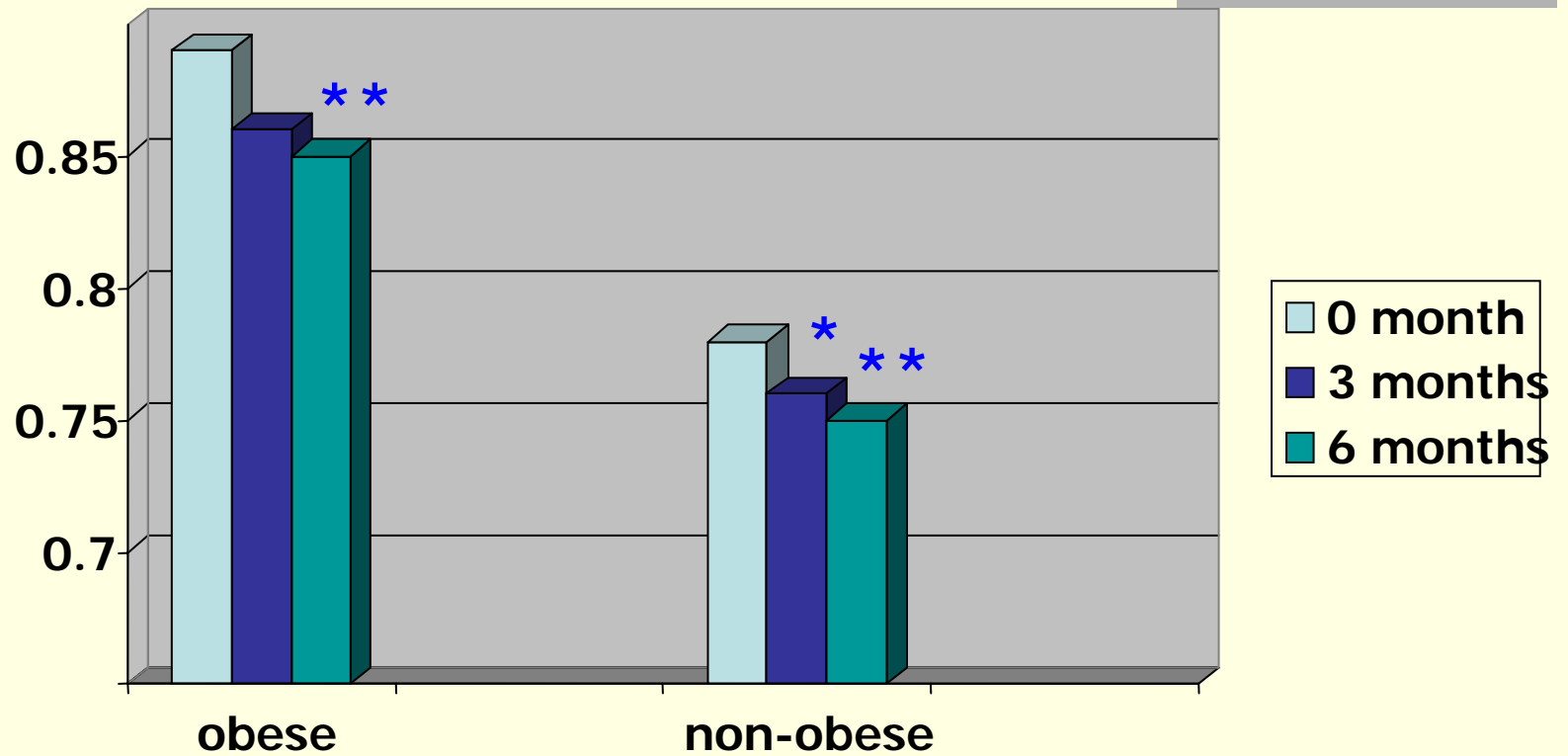
Metformin in PCOS

Treatment of the metabolic disorders



after Harborne et al 2003

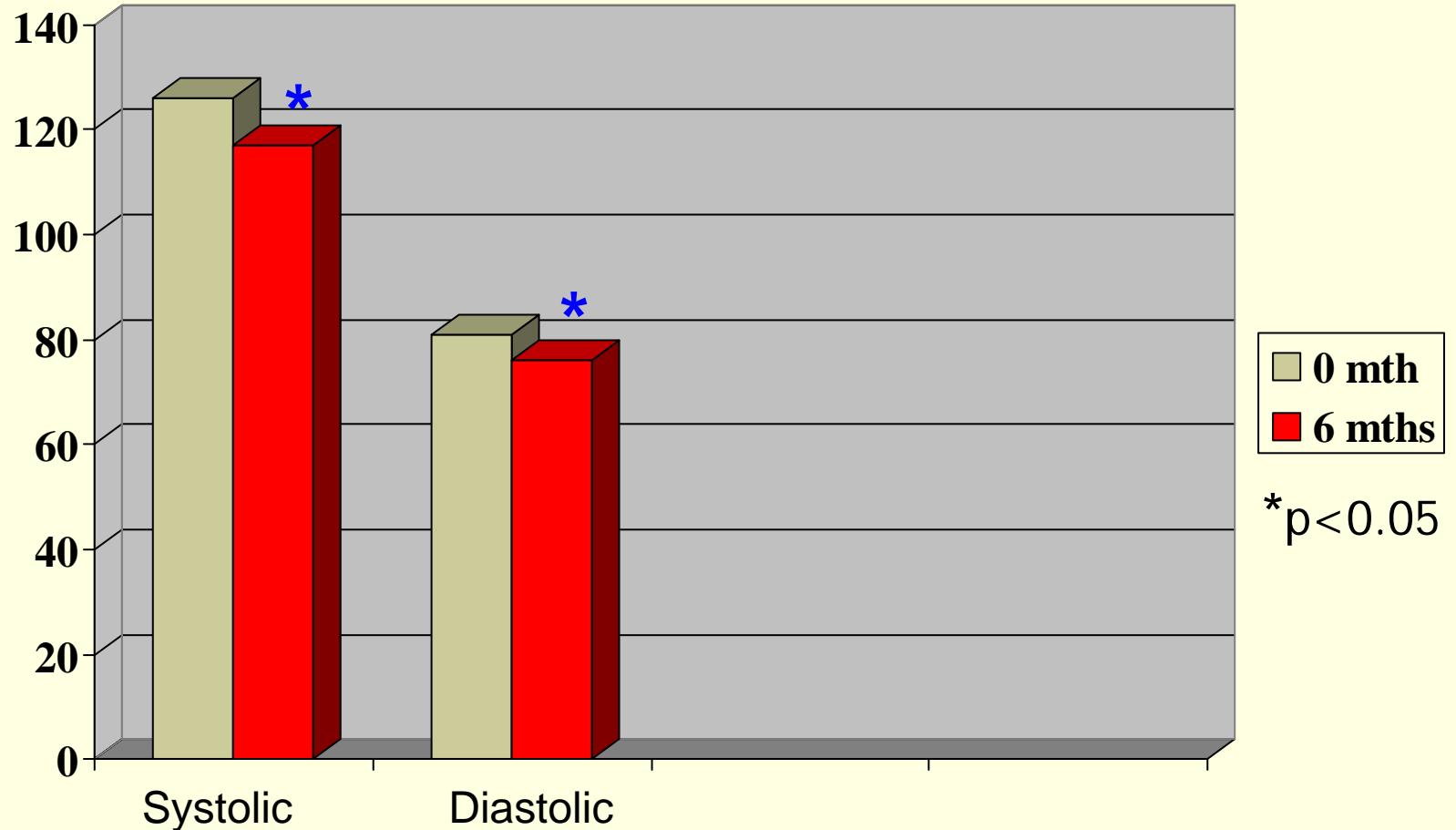
Metformin decreases WHR?



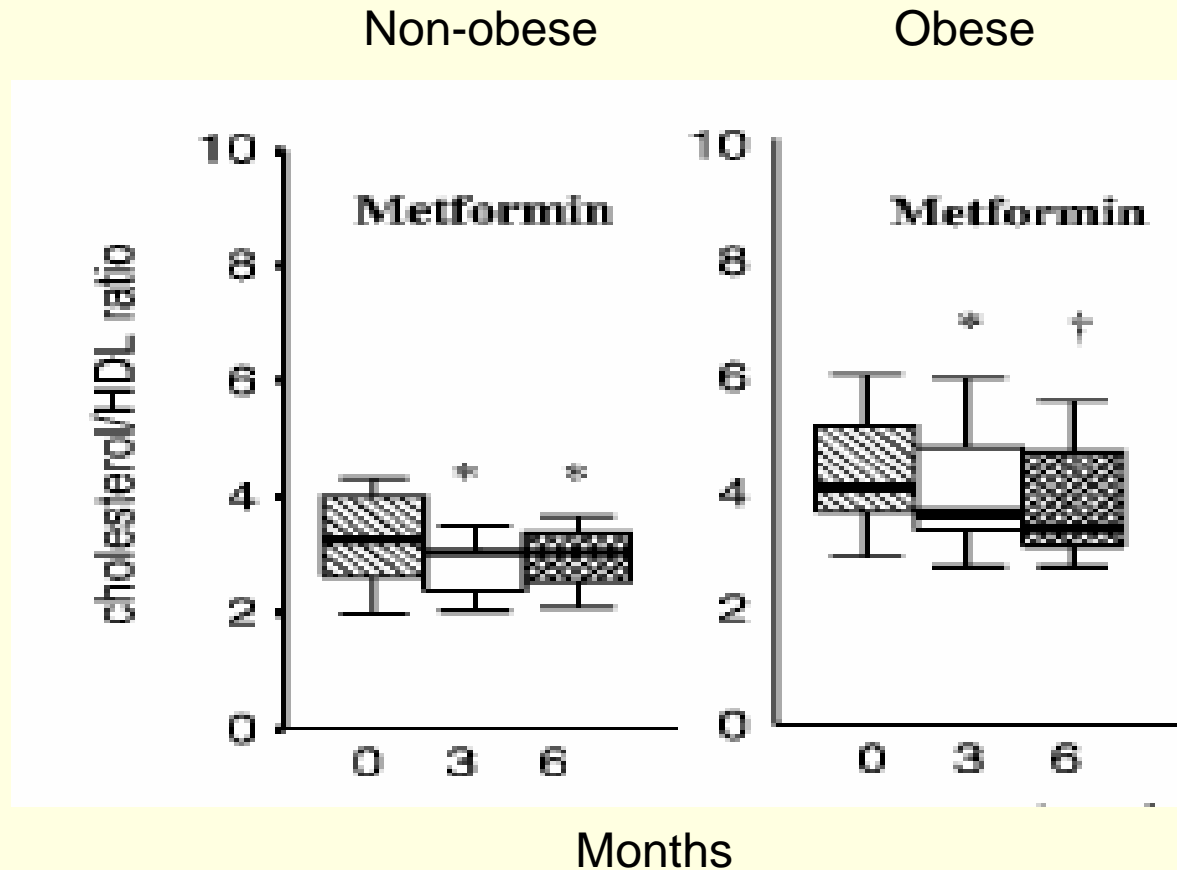
* $p < 0.05$ and ** $p < 0.01$

Morin-Papunen et al., JCEM 2000 and 2003

Metformin decreases blood pressure

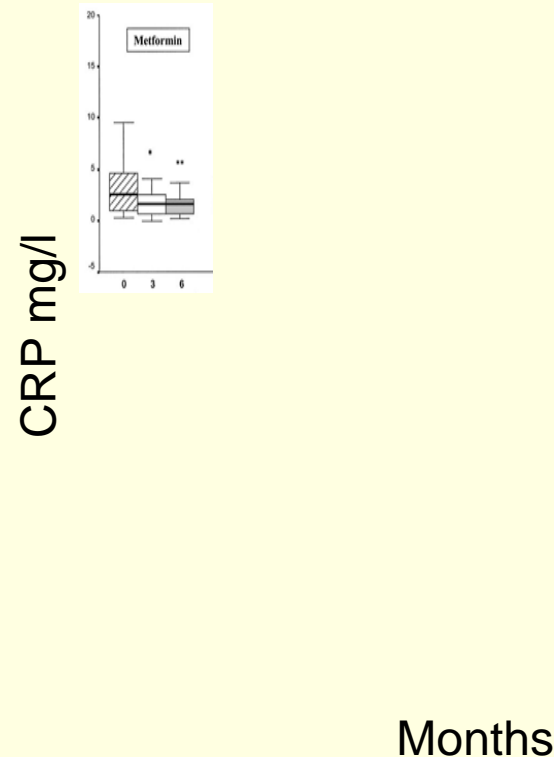


Metformin improves lipid profile



Metformin improves low-grade inflammation

- Elevated high-sensitive CRP levels - predict risk for CVD:
 - Metabolic syndrome
 - T2DM
 - PCOS
- Not only a marker - may promote endothelial dysfunction – active role in atherogenesis ?



Metformin improves low-grade inflammation *(Orio et al, 2007)*

	baseline (n=50)	after 6 months of treatment	<i>P</i>
CRP (mg/l)	1.8 ± 0.9	1.1 ± 0.6	<0.001
HDL-C (mg/dl)	45 ± 4.2	48 ± 4.6	<0.001
LDL-C (mg/dl)	87.2 ± 7.6	81.6 ± 5.3	<0.001
TG (mg/dl)	114 ± 21	112 ± 26	NS
Leukocyte count (cells/mm ³)	7050 ± 552	6080 ± 577	<0.001

Metformin improves low-grade inflammation?

- Improves endothelial dysfunction (↓endothelin -1)
- and reduces intima-media thickness of carotid arteries (*Orio 2005*)
- Controversial results
 - no effects on CRP levels (*Kjotrod 2007*)

Metformin for the prevention of metabolic complications in PCOS?

- Improves lipid profile
- Decreases chronic inflammation?

- Metformin decreases the conversion from NGT to IGT in women with PCOS (*Sharma et al 2007*)
 - **1.4%** /year vs. **16-19%** /year in the literature
 - retrospective study!
 - prospective studies needed!!

Metformin for the prevention of metabolic complications in PCOS?

- Weight loss and exercise are still the first-line treatment!
- More studies needed!



Take home message

■ **Treatment of oligo/amenorrhea**

- obese/non-obese women with metabolic disorders?

■ **Treatment of anovulation in PCOS**

- CC remains the drug of choice
- CC – resistant women → add metformin?
 - BMI > 35kg/m² → efficacy of metformin?
- more studies needed
 - combination with gonadotropins, LOD or IVF
 - decreases the risk of OHSS?
 - prevention of miscarriage, GDM or other complications of pregnancy

■ **Prevention of metabolic complications**

- large RCTs needed

Oulu PCOS team



Juha Tapanainen
Hannu Martikainen
Laure Morin-Papunen
Aimo Ruokonen
Katriina Rautio
Terhi Piltonen
Johanna Kesti
Mirja Ahvensalmi