

## Ovarian Stimulation Protocols According to Clinical Approach in a Large Danish Private Clinic, with Emphasis Put on Individual Treatments Protocols

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Based on our present knowledge about one of the most intriguing endocrinological disturbances, PCOS, different stimulation protocols used in clinically in 2001 will be revealed.

The inheritance of PCO of will be mentioned.

The endocrinology of androgen and insulin metabolism and the lipid metabolism in PCOS will be revealed and so will different forms of treatment of PCOS.

Stimulation protocols for mono ovulation and controlled ovarian hyperstimulation regimens will be elucidated. Emphasis will be put on individual stimulation protocols and the pros and cons that each protocol may yield.

## INDIVIDUAL STIMULATION BASED ON PCO-S TREATMENTS

THANKS TO THE ORGANISERS

THANKS TO YOUR FOR ATTENDING

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NORMAL



MFO



PCO



PCO described 1935; Stein - Leventhal



- CONCLUSIONS - PCO -  
- PCO IS DEFINED BY ULTRASONOGRAPHY -

PCO IS OVARIAN IN ORIGIN  
GENETIC DETERMINED  
STARTS BEFORE PUBERTY  
SEEN AMONG 20- 30%  
IS OFTEN ASSOCIATED WITH PCO-S  
OBESITY INCREASES SYMPTOMS

- OUR EXPERIENCE IS THAT THE POLYCYSTIC OVARIAN DISEASE IS THE SINGLE MOST  
UNDERDIAGNOSED CONDITION IN ENDOCRINOLOGY - HOWARD JACOBS, LONDON

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## PCO Genes

- Controlling genes
  - Folliculogenesis
  - Steroidogenesis
- Regulating genes
  - Insulin - secretion and action
  - Adipocyte function



## PCOS Genes

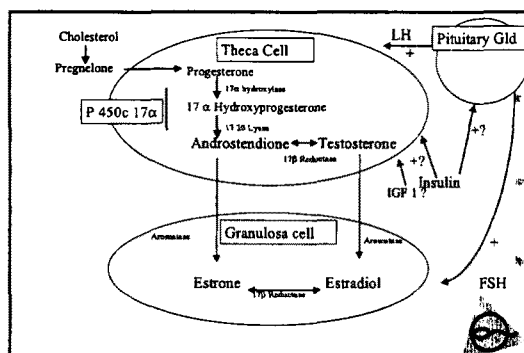
- Genetically determined
  - Folliculogenesis ?
  - Steroidogenesis - CyP11a, Chromosome 15
- Genetically Regulating
  - Insulin secretion, Chromosome 11



## PCO - Genes: 15q24 CyP11a

- p450 side chain cleavage in steroidogenesis is affected
  - ↑ Progesterone
  - ↑ 17 hydroxyprogesterone
  - ↑ Androstenedione
  - ↑ DHA





## Experimental design for PCO

- Androgens Stimulate Early stage of follicular growth
- Androgens seem to hinder early follicular atresia
- Vendola et al. J Clin Invest 1998,101,2622-2629
- ANDROGENS PROTECT SMALL FOLLICLES
- ANDROGENS INDUCE ATRESIA IN LARGE

## PCO and PCO-S ETIOLOGY

### NON-PCO

atresia of 25-35 follicles /cycle among 25 years

### PCO

Possible androgen induced non-atresia yielding continuously increasing number of follicles?

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## PCO - etiology

- Antiandrogen (Flutide)
- Normalises LH secretion

Eagleson 2000

## PCO Genes

- ↑ LH among PCO is due to permanent change in the pituitary -ovarian feed back regulation, developed in childhood or before.

Polson 1988- Modified 2001

## INSULIN and GLUCOSE

- Gene on Chromosome 11 influences insulin sensitivity
- Paternal increased segregation of this gene
  - 60% - 40% segregation instead of 50% - 50%
- Insulin or insulin resistance is related to anovulation

### INSULIN and The Ovary

- Insulin might arrest folliklar development at 8 mm Ø
- Insulin might increase stroma development in the ovary
- Insulin increases VEGF

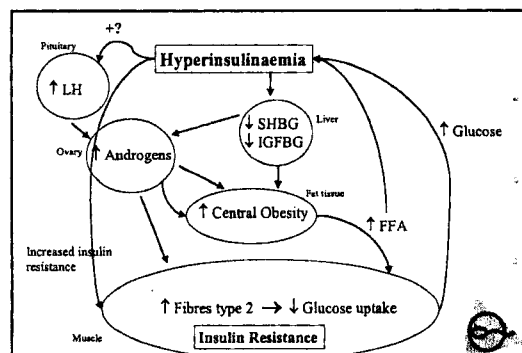
### INSULIN and Glucose

- ↑ Insulin Response on Glucose stimulation
- ↑ Insulin Resistance
- Correlation between Insulin and BMI
- Insulin sensitivity is inversely related to BMI

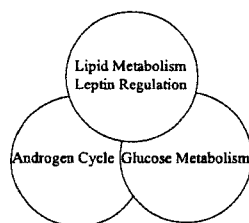
### INSULIN - Glucose

- BMI relates to triglycerides
- WHR is very important
  - Apple -/ pear form
  - Central adiposity
- HyperAndrogenism ⇒ ↑ Body Fat
  - Most likely due to Insulin resistance

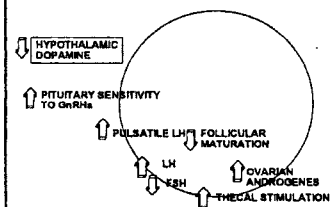
Steven Robinson

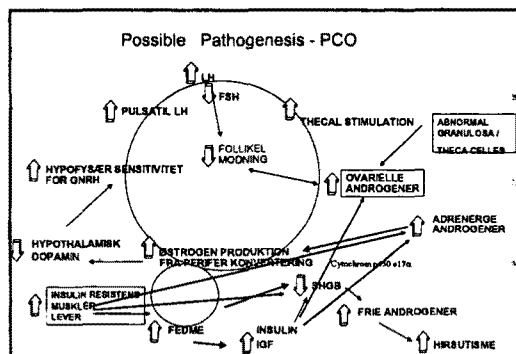
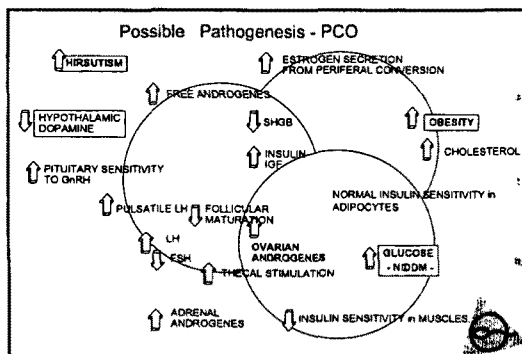
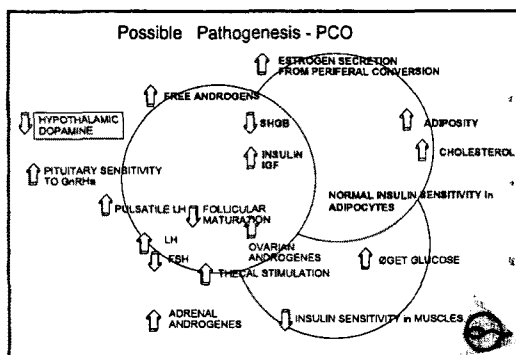
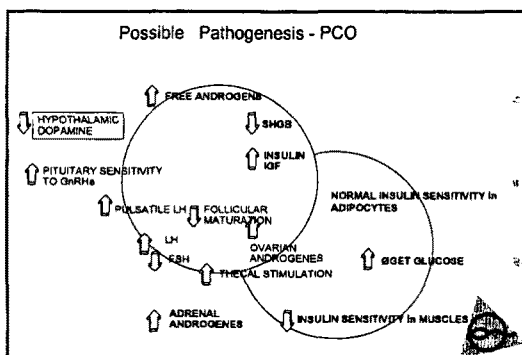


### ENDOCRINOLOGICAL RELATIONS IN PCO-S



### Possible Pathogenesis - PCO





## PCO -KNOWN AND POSSIBLE RISKS

- ADIPOSITY
- HIRSUTISM
- OLIGO-AMENORRHEA - OVULATION DEFECT
- STERILITY - DECREASED OOCYTE QUALITY
- HYPERINSULINISM OG DIABETES MELLITUS (6-7x NIDDM)
- ENDOMETRIAL CANCER - IF AMENORRHEA
- OVARIAN CANCER - IF OVULATION DEFECT ?
- MAMMARY CANCER - DUE TO ↑ INSULIN ?
- ↓ HDL OG ↑ LDL AND ↑ CVD

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## Metabolic disorders, cancer and PCO-S

- Type II Diabetes 46% at 40 years.
- 7.4 x CVD at 60 years.
- Endometrial Cancer
- Mammary Cancer ?
- Ovarian cancer ?

### Indications for treatment PCO-S

- Hirsutism
- Irregular Bleedings
- Infertility
- Adiposity, Insulin resistance .....



### Indications for treatment 1 PCO

- Hirsutism
- Ovarian suppression
- Adrenal Suppression
- Anti-androgens
- Depilation
- Local Acne therapy



### Indications for treatment 2 PCO

- Hirsutism
- Irregular Bleedings
- Cyclic Gestagen
- Oral Contraceptives
- HRT
- Metformin
- Weight loss 5 %



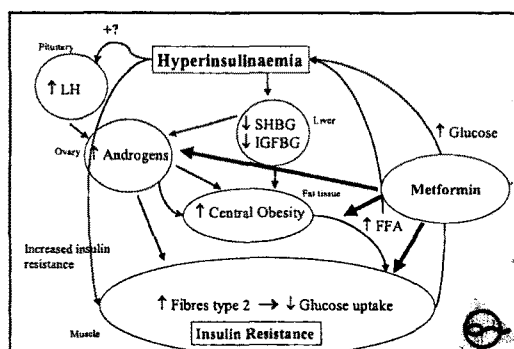
### Indications for treatment 3 PCO

- Hirsutism
- Irregular Bleedings
- Infertility
- CC
- Gonadotropins
- GnRHa- pulsatile
- Metformin a.o.?
- Dexamethazone?
- Spironolactone?
- Electrocauterisation
- Repeated stimulation?



### Indications for treatment 4 PCO

- Hirsutism
- Irregular Bleedings
- Infertility
- Adiposity, Insulin Resistance..
- Life style treatment, 30% response (Kiddy 89,92)
- Diet, Counseling, > 5 % weight loss
- Stop Cigarette smoking
- Exercise
- Metformin
- All of it ???



### Metformin - PCO-S - Obese!

- Increases weight loss
- Improves response to ovulation induction
- Improves biochemical parameters
- Improves implantation ?
- Risk of malformations ?
- Larger studies is needed

### TREATMENT OF PCO-S

- Is it possible to treat a genetic disease?
- It is manageable to treat symptoms !
- There are several ways
- Always one more than you think of

## PCO TREATMENT

- IF ANY - CLASSIC TERMS -

- **NO FERTILITY PROBLEM**
  - ORAL CONTRACEPTIVES ( ↑ SHBG)
  - CYCLIC GESTAGEN (MPA - NETA)
- **FERTILITY PROBLEM**
  - CC
  - HMG / FSH LOW DOSE STEP UP / STEP DOWN
  - ART - IUI - IVF
  - EL-COAGULATION- LAPAROSCOPICALLY

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## STIMULATION

- STEP BY STEP -

- **SCANNING: OVARIES + ENDOMETRIUM**
  - LEARN TO KNOW THE PATIENT - INITIAL FSH?
- **START SAFE**
  - CC - combined ± combination with LOW DOSE FSH better than HMG ? Endometrium !
- Possible Luteal Support
- LUF ?
- IVF is often imminent

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## STIMULATION

- What Patient? -

- **Ultrasonography: OVARIES + ENDOMETRIUM**
  - Large Ovaries: > 30 mm Take care
  - Normal Ovaries: 20 - 30 mm: standard dose
  - Small Ovaries: < 20 mm: Problems
- **FSH - (Inhibin a / b)**
  - FSH < 7: OK
  - FSH > 10: Problems
  - FSH > 15 Serious Problems
- **Age:**
  - < 30 !
  - > 35
  - > 40 / 43!!!!

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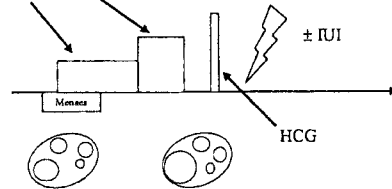
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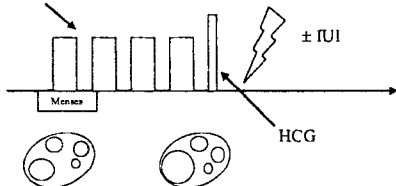
### Mono Ovulation - PCO

- **Thick endometrium**  
Try CC - Possible in combination with FSH
- **Thin endometrium or failure with CC**  
Low dose step up  
Low dose step up and step down  
Step down protocol

### CC - FSH / Mono-ovulation or COHS



### FSH / Mono-ovulation or COHS



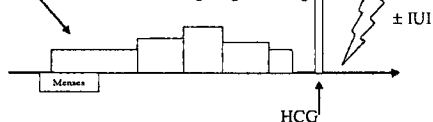
### FSH / Mono-ovulation for PCO-S

Low dose step up



### FSH / Mono-ovulation for PCO-S

Low dose step up - step down



### Puregon Pen

